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Exposure to antiretroviral therapy in uninfected children born to HIV infected women in Europe

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Declaration

I, Claire Dominique Hankin, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This thesis aims to investigate possible adverse side effects of antiretroviral therapy (ART) exposure in uninfected children born to HIV infected women, and to explore potential strategies for monitoring the health of these children. Using data from the European Collaborative Study, an ongoing multi-centre cohort study of HIV infected women and their children, the association between ART exposure and health outcomes in uninfected children was investigated. ART exposure was not associated with congenital abnormalities, or serious clinical symptoms up to 18 months of age. Children exposed to combination therapy were more likely to be premature than unexposed children. There was a marginal but significant negative effect of combination therapy exposure on weight, height and head circumference up to 18 months of age, when compared to no or monotherapy exposure. The CHART study, a consented clinic-based follow-up of uninfected children born in the UK, was conducted for three years to explore the feasibility of individualised follow-up to monitor adverse health events. The study was based on reports to obstetric and paediatric HIV surveillance, the National Study of HIV in Pregnancy and Childhood (NSHPC). Of 2104 eligible children, 33% were enrolled, 25% lost to follow-up, parents of 5% declined and the remainder could not be enrolled mainly because of resources or family circumstances. To obtain details on deaths and cancers among ART-exposed children over the long term, nearly 2200 uninfected children reported to the NSHPC were identified on the National Health Service Central Register through an anonymous matching procedure. Three deaths and no cancers were notified by the end of 2005. A survey of 140 parents and carers of ART-exposed uninfected children was conducted to seek their views on the long-term follow-up of their children. Although most respondents were supportive of the rationale for follow-up, contradictory views were expressed on how contact should be maintained.

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Role of the Researcher

The National Study of HIV in Pregnancy and Childhood (NSHPC) and the European Collaborative Study (ECS) are based at the Institute of Child Health in London. I have been involved with both studies since 2001 and have taken a major role in elements of both as detailed below. The studies are outlined in Chapter 2.

National Study of HIV in Pregnancy and Childhood

I collaborated closely with colleagues working on the NSHPC to identify children eligible for the CHART study and the Office for National Statistics (ONS) flagging study (see below). I also assisted with data collection and clarification of reports made to the NSHPC.

Follow up of uninfected children born to HIV infected women in the UK: the CHART study (Chapter 7)

I was the designated researcher on the CHART study. I wrote the information sheets for parents and health professionals, and designed the questionnaire. I was responsible for the management of the study, correspondence with health professionals and processing returned forms. I designed a database for the management of the study and for data storage, and I was responsible for data entry and analysis. During the course of the study it was necessary to renew ethics approval for the study, and I prepared the Multi-centre Research Ethics Committee (MREC) application. Enrolment in the study closed in June 2005, and I am currently drafting papers arising from the study as well as a report for the Medical Research Council.

Office for National Statistics flagging study (Chapter 6)

I was the researcher responsible for this study. I developed a protocol for identifying children reported to the NSHPC on the National Health Service Central Register (NHSCR) in order to receive reports of death or cancer in those individuals over the longer term (known as a "flagging study"). I extracted and cleaned data from the NSHPC database, worked with colleagues at ONS to develop an appropriate algorithm for matching NSHPC cases with births on the Births/Deaths Registration Database (BDRD), and devised a confirmatory programme to identify cases to be flagged on the NHSCR.

Health professional survey (Chapters 7 and 8)

I initiated the survey, designed the questionnaire and was responsible for the survey administration. I designed the database, and entered and analysed the data.

Parent and carer survey (Chapter 8)

I initiated the survey, developed the protocol, wrote the information sheet and designed the questionnaire. I also prepared the MREC application. I was responsible for the survey administration and I attended six London clinics on 33 occasions to administer the questionnaire. I designed the database, and entered and analysed the data.

<u>European Collaborative Study (Chapters 3-5)</u>

In the analyses conducted using data from the ECS, I was responsible for the data cleaning and data analysis. I drafted the manuscripts for publication (see below) and corresponded with ECS collaborators.

Publications arising from the research

European Collaborative Study (Prepared by Hankin C, Thorne C, Peckham C, Newell M). Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr.* 2003; 32(4): 380-387.

European Collaborative Study (Prepared by Hankin C, Thorne C, Peckham C, Newell M). The health and social environment of uninfected infants born to HIV-infected women. *AIDS Care.* 2004; 16(3): 293-303.

Hankin CD, Tookey PA, Lyall EGH, Peckham CS. Follow up of children exposed to antiretroviral therapy in pregnancy (CHART). Royal College of Paediatrics and Child Health 8th Spring Meeting, York, UK, 2004. *Arch Dis Child.* 2004; 89 (Suppl 1): A76.

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Hankin C, Cross R, Seery P, Gurtin D. Parents' views on long-term follow-up of uninfected children born to HIV-infected women and exposed to antiretroviral therapy. Royal College of Paediatrics and Child Health 10th Spring Meeting, York, UK, 2006. *Arch Dis Child.* 2006; 91 (Suppl 1): A69.

Hankin CD, Lyall EGH, Masters JI, Peckham CS, Tookey PA. Feasibility of clinic-based follow-up of uninfected children born to HIV-infected women in the UK: the children

exposed to antiretroviral therapy study (CHART). XVI International AIDS Conference, Toronto, Canada, 2006. [Accepted].

Hankin C, Newell M, Tookey P. Parents' and health professionals' views on the long-term follow-up of uninfected children born to HIV-infected women and exposed to antiretroviral therapy. [In preparation].

Hankin CD, Lyall EGH, Peckham CS, Tookey PA. Monitoring death and cancer in children born to HIV-infected women in England and Wales: use of HIV surveillance and national routine data. [In preparation].

Hankin CD, Lyall EGH, Peckham CS, Tookey PA. Feasibility of clinic-based follow-up of uninfected children born to HIV-infected women in the UK: the CHART study. [In preparation].

Hankin CD, Lyall EGH, Peckham CS, Tookey PA. Exposure to antiretroviral therapy in uninfected children born to HIV-infected women in the UK. [In preparation].

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Finally I want to thank all my family and friends for their constant support and encouragement.

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Acronyms and abbreviations

3TC	Lamivudine
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
BDRD	Births/Deaths Registration Database
BPSU	British Paediatric Surveillance Unit
CD4 cell	T-helper lymphocyte
CHART study	Follow up of uninfected children born to HIV infected women in the UK
ECS	European Collaborative Study
GP	General practitioner
GRO	General Register Office
GU	Genitourinary
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
ICH	Institute of Child Health
IDU	Illicit drug use
MTCT	Mother-to-child transmission
NHS	National Health Service
NHSCR	National Health Service Central Register
NN4B	National Health Service "Numbers for Babies" initiative
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSHPC	National Study of HIV in Pregnancy and Childhood
OFC	Occipitofrontal circumference
ONS	Office for National Statistics

PACTG	Pediatric AIDS Clinical Trials Group
PCR	Polymerase chain reaction
PI	Protease inhibitor
RCOG	Royal College of Obstetricians and Gynaecologists
RCPCH	Royal College of Paediatrics and Child Health
UA	Unlinked anonymous (use of residual anonymised blood for HIV testing)
UK	United Kingdom
ZDV	Zidovudine

Chapter 1 HIV infection in women and children

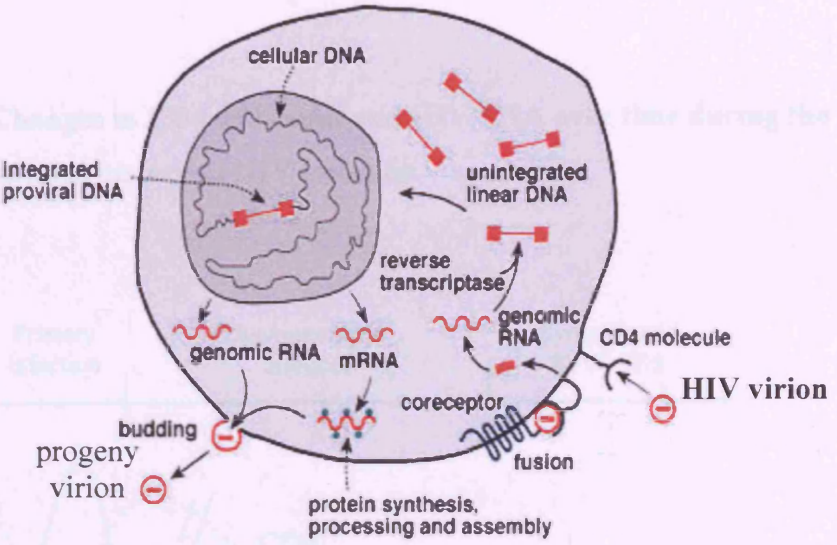
1.1 HIV infection

Acquired immune deficiency syndrome (AIDS) consists of a range of opportunistic infections and cancers that are associated with immunodeficiency. AIDS was first recognised in the USA in 1981 (Gottlieb *et al.* 1981). The causative agent of AIDS is the human immunodeficiency virus (HIV), which was identified in France in 1983 (Barre-Sinoussi *et al.* 1983).

HIV is a retrovirus belonging to the genus lentivirus. The most common species of HIV is HIV-1. The main target cell of HIV is the CD4+ T-lymphocyte (CD4 cell), a major cell of the immune system. HIV replication begins when a virion binds to a CD4 receptor and one of two co-receptors on the host cell (see Figure 1.1). After fusion with the cell, ribonucleic acid (RNA) from the virion is released into the cytoplasm. RNA is then converted to deoxyribonucleic acid (DNA), through reverse transcription. The DNA then enters the nucleus and is integrated into the cell DNA. Viral production begins when messenger RNA (mRNA) and genomic RNA are formed. mRNA is used to make viral proteins which are then split into smaller proteins by the enzyme protease. A progeny virion is assembled from the genomic RNA and the proteins; it is then ejected from the host cell (Phoolcharoen and Detels 2002).

HIV infection is associated with a progressive reduction in CD4 cells and a parallel increase in plasma HIV RNA (viral load). The clinical course of the infection typically includes three stages (see Figure 1.2). Primary infection is a period of rapid viral replication that persists for several weeks until an immune response occurs and HIV antibodies are produced (seroconversion).

Figure 1.1 The replication cycle of HIV



Source: (National Institute of Allergy and Infectious Diseases 2006)

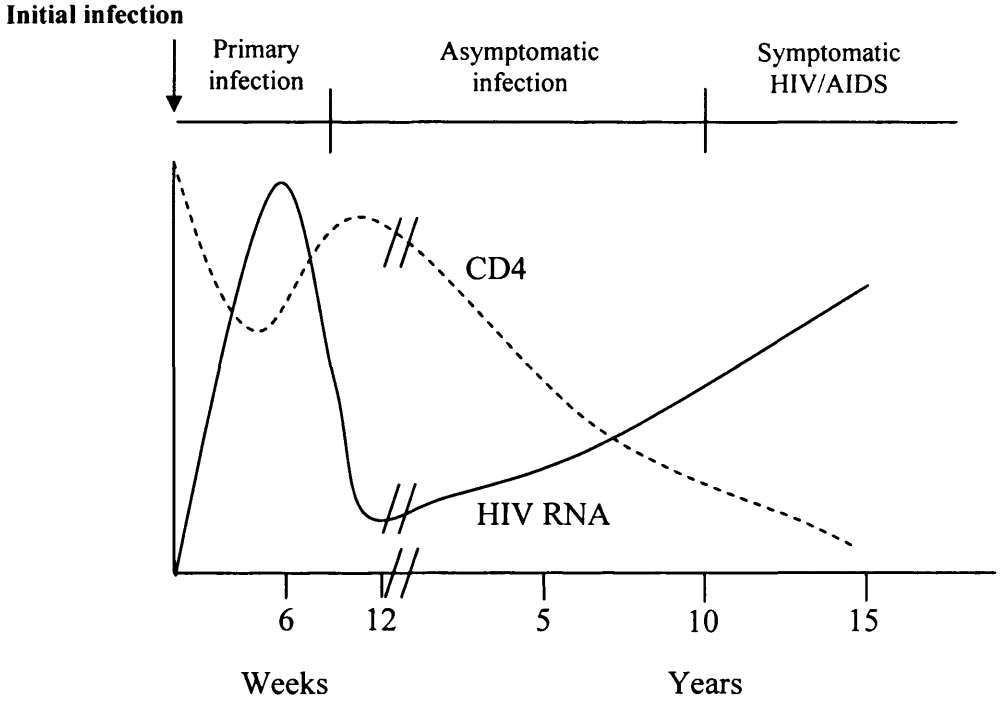
Although the following asymptomatic period can last for many years and is one of clinical latency, there is still continued viral turnover. Later in the course of the infection, HIV symptoms develop, which include weight loss, fungal infections and fevers. This is followed by an AIDS diagnosis: an opportunistic infection, cancer, HIV dementia or wasting syndrome (Centers for Disease Control and Prevention 1992).

In developed countries, median time from primary infection to the development of AIDS in untreated individuals is around 10 years (Munoz *et al.* 1989, Goedert *et al.* 1989). Death then usually occurs within two years (Mocroft *et al.* 1997, Rothenberg *et al.* 1987).

CD4 cell count and viral load are used as prognostic indicators of HIV disease progression. The most widely used system for classifying HIV infection and AIDS in

adults was published by the Centers for Disease Control and Prevention in 1992 (Centers for Disease Control and Prevention 1992).

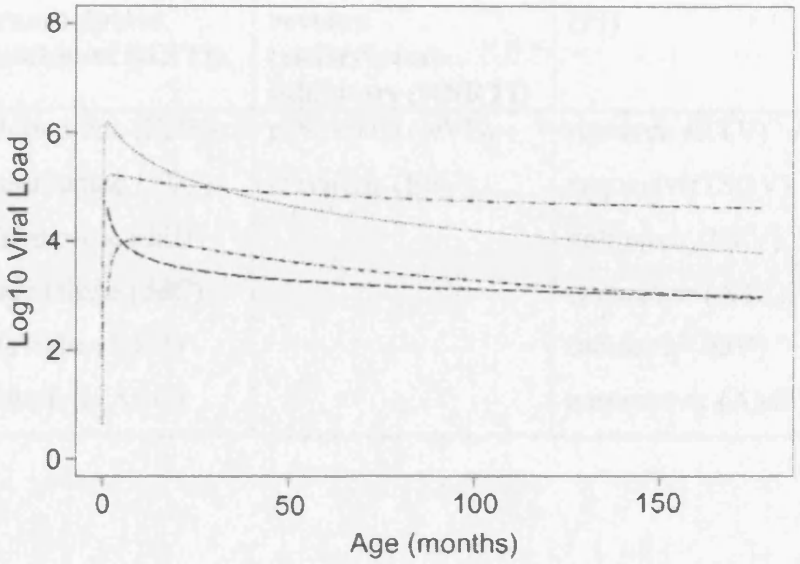
Figure 1.2 Changes in CD4 cell count and HIV RNA over time during the natural history of HIV infection



Source: (Luzzi *et al.* 2003)

HIV RNA viral load in children with vertically-acquired HIV infection (see Section 1.5) peaks soon after birth and then gradually declines thereafter (Figure 1.3) (European Collaborative Study 2002). The slower decline in viral load in infants compared with adults is likely to be due to the immaturity of the infant immune system. In terms of CD4 cell counts in HIV infected children, data from Europe have shown a peak at seven weeks of age, with a subsequent decrease over the first few years of life (European Collaborative Study 2003a).

Figure 1.3 Log RNA viral load in HIV infected children by age, sex and antiretroviral treatment



..... Females (no and monotherapy) ---------- Females (combination therapy)
_..._..._... Males (no and monotherapy) -.-.-.-.-.-.- Males (combination therapy)

Source: (European Collaborative Study 2002)

1.2 Antiretroviral therapy

The first antiretroviral drug used for the treatment of HIV infection was zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI), made available in 1987 (Fischl *et al.* 1987). Additional NRTIs and three further drug classes: non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and fusion inhibitors (FI), were subsequently developed (Table 1.1).

Large randomised clinical trials in the mid 1990s demonstrated the clinical superiority of using double therapy over monotherapy (Delta Coordinating Committee 1996, Hammer *et al.* 1996). Highly active antiretroviral therapy (HAART) was later shown to delay HIV disease progression further (Collier *et al.* 1996). HAART consists of at least three antiretroviral drugs used in combination, usually including a PI or NNRTI with two NRTIs.

Table 1.1 Principal antiretroviral drugs

Nucleoside reverse transcriptase inhibitors (NRTI)	Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Protease inhibitors (PI)	Fusion inhibitors (FI)
zidovudine (ZDV)	nevirapine (NVP)	ritonavir (RTV)	enfuvirtide (T-20)
lamivudine (3TC)	efavirenz (EFV)	saquinavir (SQV)	
didanosine (ddI)		nelfinavir (NFV)	
zalcitabine (ddC)		atazanavir (ATZ)	
stavudine (d4T)		indinavir (IDV)	
abacavir (ABC)		amprenavir (AMP)	

HAART was introduced in 1996 and its use soon became widespread in Europe (Kirk *et al.* 1998, CASCADE Collaboration 2000, Mocroft *et al.* 1998). HAART has become the standard of care for HIV infected individuals in resource-rich settings (Gazzard 2005). Of over 41 000 patients seen for HIV care in the UK in 2004, 64% were receiving three or more antiretroviral drugs, compared with 1% on monotherapy or double therapy; and a third of patients were not on therapy (The UK Collaborative Group for HIV and STI Surveillance 2005).

The use of HAART has consistently been shown to improve survival in HIV infected individuals in both clinical trials (Hammer *et al.* 1997) and observational studies (Murphy *et al.* 2001). An analysis of nearly 10 000 patients in the EuroSIDA study showed that there was a reduced risk of AIDS in the late HAART era (1998-2002) compared with the early HAART era (1996-1997) (Mocroft *et al.* 2003). European HIV/AIDS surveillance has shown a reduction in AIDS diagnoses and mortality associated with AIDS over the last 10 years (European Centre for the Epidemiological Monitoring of AIDS 2005).

Initiation of antiretroviral therapy (ART) depends on clinical and immunological staging of HIV disease. The combination of antiretroviral drugs used depends on factors such as potential drug interactions, toxicity, resistance and adherence. Antiretroviral drugs delay progression of disease by interrupting HIV replication (see Figure 1.1). NRTIs resemble nucleotides that are used to form DNA during reverse transcription. When reverse transcriptase takes up an NRTI instead of a natural nucleotide, growth of the DNA chain ceases. NNRTIs bind directly to reverse transcriptase and prevent it from adding natural nucleotides to the DNA chain. PIs block the activity of protease, therefore preventing viral proteins from being split up, and ultimately halting the assembly of progeny virions. FIs prevent glycoproteins from attaching to the host cell, consequently averting fusion of the virion.

1.3 Epidemiology of HIV infection

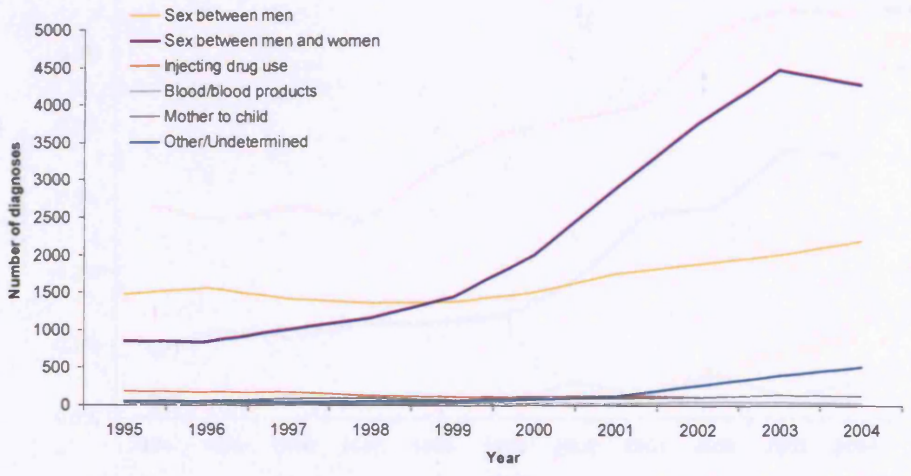
By the end of 2005 an estimated 40.3 million people were living with HIV worldwide, just under half of whom were female. Two thirds of people living with HIV were in sub-Saharan Africa (25.8 million) (UNAIDS/WHO 2005).

In western Europe, over 20 000 newly diagnosed HIV infections, 35% of which were in females, were reported to European HIV/AIDS surveillance in 2004 (European Centre for the Epidemiological Monitoring of AIDS 2005). By the end of 2004, over 71 000 HIV infections were known to have been diagnosed in the UK since the early 1980s; and the annual total increased from nearly 4000 in 2000, to just over 7000 in 2004 (The UK Collaborative Group for HIV and STI Surveillance 2005).

The main routes through which HIV is transmitted are: sexual contact, exposure to blood or blood products, and mother-to-child transmission (MTCT). Initially the majority of

cases of HIV and AIDS were in homosexual males and injecting drug users. Globally, heterosexual contact is now the predominant mode of transmission, particularly in sub-Saharan Africa and areas such as South-East Asia (UNAIDS/WHO 2005). MTCT is the dominant type of acquisition for children (see Section 1.5). In western Europe, 56% of newly diagnosed HIV infections reported in 2004 were through heterosexual contact, 30% were in homosexual or bisexual men, and 10% were in injecting drug users. Almost all women were infected through heterosexual contact (91%) (European Centre for the Epidemiological Monitoring of AIDS 2005). The increase in numbers of HIV diagnoses in the UK in recent years (see Figure 1.4), has been mainly due to increased diagnosis of infections acquired through heterosexual contact in high-prevalence areas, particularly sub-Saharan Africa (The UK Collaborative Group for HIV and STI Surveillance 2005).

Figure 1.4 HIV diagnoses by exposure group, UK: 1995-2004



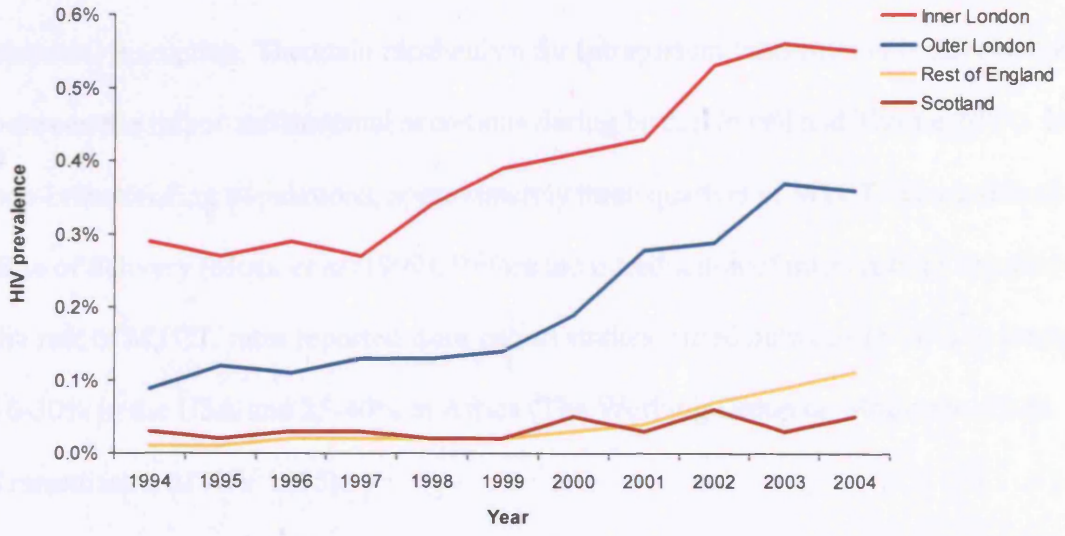
Numbers will rise for recent years, as further reports are received. **Data Source:** HIV/AIDS diagnoses reports, United Kingdom.

Source: (The UK Collaborative Group for HIV and STI Surveillance 2005)

1.4 HIV infection in pregnant women

The prevalence of HIV infection in pregnant women, regardless of diagnosis status, can be assessed through unlinked anonymous (UA) testing of either blood samples from pregnant women or residual infant dried blood spots (for maternal HIV antibodies). In western Europe, reported prevalence of HIV infection in pregnant women between 1995 and 2000 ranged from <0.02% (Finland, Sweden, Norway) to 0.15% (Spain) (European Centre for the Epidemiological Monitoring of AIDS 2001). Prevalence of HIV infection in women giving birth in England and Scotland has increased dramatically in recent years: from 0.09% in 2000 to 0.18% in 2004 (The UK Collaborative Group for HIV and STI Surveillance 2005) (Figure 1.5).

Figure 1.5 HIV prevalence[1] among pregnant women by area of residence (England and Scotland)



[1]Includes previously diagnosed, those diagnosed through antenatal screening and those remaining undiagnosed
Data source: Unlinked anonymous testing of newborn infant dried blood spots, England and Scotland

Source: (The UK Collaborative Group for HIV and STI Surveillance 2005)

HIV infected pregnant women are only able to access interventions to prevent MTCT (described in Section 1.5) when they are aware of their infection status. The estimated proportion of HIV infected pregnant women diagnosed before delivery in England and Scotland has increased from 71% in 2000 to 92% in 2004 (The UK Collaborative Group for HIV and STI Surveillance 2005). This is mainly due to the widespread offer and recommendation of routine antenatal HIV testing since 1999 (NHS Executive 1999), and the increase in the number of women already diagnosed becoming pregnant (Cliffe *et al.* 2001).

1.5 Mother-to-child transmission of HIV infection

1.5.1 Rates and risk factors

MTCT (or vertical transmission) of HIV can occur during pregnancy, delivery or in the postnatal period through breastfeeding. Intrauterine transmission may occur due to fetal exposure to the virus in the amniotic fluid, or due to infection of placental cells and/or placental disruption. The main mechanism for intrapartum transmission is direct contact between the infant and maternal secretions during birth (Newell and Thorne 2004). In non-breastfeeding populations, approximately three quarters of MTCT occurs around the time of delivery (Mock *et al.* 1999). Before the introduction of interventions to reduce the risk of MTCT, rates reported from cohort studies varied between 15-20% in Europe, 16-30% in the USA and 25-40% in Africa (The Working Group on Mother-to-Child Transmission of HIV 1995).

Maternal plasma HIV RNA level is the strongest independent risk factor for MTCT, and this has been shown both in cohort studies (Cooper *et al.* 2002, European Collaborative Study 2005c) and in clinical trials (Shaffer *et al.* 1999). Clinical risk factors such as AIDS are indirect markers for viral load (Newell and Thorne 2004). Other risk factors

for MTCT include CD4 cell count, obstetric factors such as vaginal delivery and prolonged rupture of membranes (Landesman *et al.* 1996, Kind *et al.* 1998), premature delivery (European Collaborative Study 1999) and breastfeeding (Dunn *et al.* 1992).

1.5.2 Interventions

Avoidance of breastfeeding significantly reduces the risk of MTCT; and HIV infected women in resource-rich settings are recommended to exclusively formula feed (Hawkins *et al.* 2005). ART prophylaxis is a highly effective intervention. Results from the Pediatric AIDS Clinical Trial Group (PACTG) 076 trial in the USA, published in 1994, showed that ZDV given to HIV infected pregnant women during pregnancy and delivery and to the neonate for six weeks, reduced the risk of MTCT by two thirds (Table 1.2) (Connor *et al.* 1994). The protocol was soon adopted as routine clinical practice across Europe (European Collaborative Study 2001). ART reduces the risk of MTCT by decreasing viral replication and therefore viral load in the pregnant woman, and acting as a prophylaxis for the neonate. Other clinical trials have shown the efficacy of more simple and less expensive strategies, such as short-course ZDV and single-dose nevirapine, for use in less developed countries (Table 1.2) (Shaffer *et al.* 1999, Guay *et al.* 1999, World Health Organization 2004).

Over the last 10 years, there has been a shift from ZDV monotherapy to HAART use for HIV infected pregnant women (Cooper *et al.* 2002). This has reflected changes in the management of HIV disease in adults (Mocroft *et al.* 2003, Kirk *et al.* 1998). Although never evaluated in a randomised placebo-controlled trial, HAART is effective in reducing the risk of MTCT by lowering viral load. Cohort studies have shown very low rates of MTCT in the HAART era (Cooper *et al.* 2000, European Collaborative Study 2005c).

Table 1.2 Clinical trials of antiretroviral therapy to prevent mother-to child transmission

Trial	Reference	Setting	Trial design	Infant feeding	Therapy		Transmission rate
					Antenatal / intrapartum	Neonatal	
PACTG 076	1	USA & France	Randomised, placebo-controlled	Formula	AN: ZDV (from 14-34 weeks) IP: intravenous ZDV	ZDV for 6 weeks	8.3% in ZDV arm versus 25.5% in placebo arm at 18 months
Bangkok short-course ZDV	2	Thailand	Randomised, placebo-controlled	Formula	AN: ZDV (from 36 weeks) IP: oral ZDV	None	9.4% in ZDV arm versus 18.9% in placebo arm at 6 months
ANRS 075	3	France	Open label, non-randomised	Formula	AN: ZDV (from 14 weeks) + 3TC (from 32 weeks) IP: intravenous ZDV + oral 3TC	ZDV + 3TC for 6 weeks	1.6%
HIVNET 012	4 & 5	Uganda	Randomised, placebo-controlled NVP versus ZDV	Breast	AN: none IP: oral sdNVP versus oral ZDV	sdNVP within 72 hours of birth versus ZDV for 7 days	15.7% in NVP arm versus 25.8% in ZDV arm at 18 months. Placebo arm stopped

PACTG, Pediatric AIDS Clinical Trial Group; ANRS, Agence Nationale de Recherches sur le SIDA; HIVNET, HIV Network for Prevention Trials; AN, antenatal; IP, intrapartum; ZDV, zidovudine; sdNVP, single dose nevirapine; 3TC, lamivudine

References:

1) (Connor *et al.* 1994)
2) (Shaffer *et al.* 1999)
3) (Mandelbrot *et al.* 2001)
4) (Guay *et al.* 1999)
5) (Jackson *et al.* 2003)

Elective caesarean section before the onset of labour and rupture of membranes reduces the risk of MTCT compared with a vaginal delivery, as the procedure prevents contact between the fetus and maternal secretions. The protective effect of an elective caesarean section was reported in observational studies (Mandelbrot *et al.* 1998) and a randomised clinical trial (The European Mode of Delivery Collaboration 1999). However, the low MTCT rates achieved with HAART use during pregnancy have led to a debate about whether an elective caesarean section brings any added benefits in terms of a reduced risk of MTCT, particularly as there are risks associated with the procedure itself (Fiore *et al.* 2004).

When interventions are used in combination, MTCT rates can be reduced from between 15-20% in the absence of any interventions (The Working Group on Mother-to-Child Transmission of HIV 1995) to less than 2% (European Collaborative Study 2005c, European Collaborative Study 2001, Mandelbrot *et al.* 1998, Kind *et al.* 1998). The success of interventions is evident in the reduction of reported paediatric HIV infections (Tookey 2005b, Hamers and Downs 2004).

1.6 Antiretroviral therapy exposure and potential adverse effects in children

Concern has been raised regarding the risk of adverse effects in children exposed to ART *in utero* and/or in the neonatal period (Mofenson and Munderi 2002). Long-term permanent toxicities have been reported in some epidemiological and animal studies (Blanche *et al.* 1999, Olivero *et al.* 2002). The need to assess adverse effects is particularly important in uninfected children due to their increasing numbers (Tookey 2005b), and the fact that they are likely to be discharged from paediatric care when they are confirmed uninfected (usually around 18 months of age) (Newell *et al.* 2002). HIV

infected women are taking increasing numbers of drugs and drug combinations during pregnancy (European Collaborative Study 2005c, Townsend *et al.* 2006). HAART is often started before HIV symptoms develop, therefore women may be already on therapy when they conceive; and HIV infected pregnant women are recommended to use ART for their own health if appropriate (Hawkins *et al.* 2005, Public Health Service Task Force 2005a).

Information about the safety of ART exposure in children born to HIV infected women comes mainly from multi-centre cohort studies such as the European Collaborative Study (ECS) (European Collaborative Study 2004b), the French Perinatal Cohort Study (Le Chenadec *et al.* 2003) and the Women and Infants Transmission Study (WITS) (Cooper *et al.* 2002); and MTCT trials such as the PACTG trials (Sperling *et al.* 1998) and the Thai trials (Chotpitayasunondh *et al.* 2001). Animal studies also provide information on potential adverse effects (Olivero *et al.* 1997).

1.6.1 Congenital abnormalities

Teratogenicity studies have been carried out on individual antiretroviral drugs. Fetal malformations have been reported in rats given near lethal doses of ZDV; and significant central nervous system malformations were observed in 3 out of 20 monkeys exposed to efavirenz *in utero*. Abacavir and zalcitabine have also been associated with an increased risk of malformations in rats (Public Health Service Task Force 2005b, Thorne and Newell 2005).

There have been case reports of congenital abnormalities in humans exposed to efavirenz *in utero*. These include neural tube defects and spinal malformations (Fundaro *et al.* 2002, De Santis *et al.* 2004). Due to these reports and the teratogenic findings in

primates, it is recommended that efavirenz is not taken in the first trimester of pregnancy, the primary period of fetal organogenesis (Public Health Service Task Force 2005b).

The possibility of a synergistic effect of combination therapy and folate antagonists prescribed for *Pneumocystis carinii* pneumonia (PCP) prophylaxis has been raised. Severe spinal malformations have been reported in the fetuses of two women in the UK (Richardson *et al.* 2000). In a retrospective case note review, Jungmann *et al.* found exposure to both combination therapy and folate antagonists in the first trimester was associated with an increased risk of congenital abnormalities (Jungmann *et al.* 2001). However the study was relatively small with 195 mother-child pairs and this association has not been reported elsewhere.

In the PACTG 076 trial, no differences in structural abnormalities between infants in the study drug arm and those in the placebo arm were observed (Table 1.3) (Sperling *et al.* 1998). An analysis on over 3500 mother-child pairs from the ECS found no evidence to suggest that exposure to first trimester ART, including HAART, increased the risk of congenital abnormalities (European Collaborative Study 2005a). Furthermore, recent data from obstetric and paediatric HIV surveillance in the UK and Ireland on over 3000 infants born to HIV infected women, showed no statistically significant association between the prevalence of congenital abnormalities and exposure to ART. Prevalence was similar regardless of whether exposure occurred in the first trimester (Townsend *et al.* 2006).

Table 1.3 Antiretroviral therapy exposure and potential adverse effects in children: follow-up data from mother-to-child transmission clinical trials

Study (Reference)	Setting	Number of HIV-exposed children	Follow- up	ART exposure (n)	Main adverse effects addressed	Findings
PACTG 076 (1)	USA & France	417	342 (82%) followed up to 18 months of age	PACTG 076 protocol* (209) Placebo group (208)	Anaemia	More common in ZDV group
					Structural abnormalities	No difference
					Growth	No difference
					Immunologic function	No difference
PACTG 076/219 (2)	USA	234 (uninfected children)	Median age at last follow-up 4.2 years (range 3.2-5.6)	PACTG 076 protocol* (122) Placebo group (112)	Deaths & malignancies	None
					Growth	No difference
					Immunologic function	No difference
BCPHTSG (3)	Thailand	395	319 (81%) followed up to 18 months of age	Bangkok protocol# (196) Placebo group (199)	Growth	No difference
					Immunologic function	No difference
					Malignancies	None

PACTG, Pediatric AIDS Clinical Trials Group; BCPHTSG, Bangkok Collaborative Perinatal HIV Transmission Study Group; ZDV, zidovudine
*PACTG 076 protocol: antepartum oral ZDV initiated at 14-34 weeks gestation and continued for duration of pregnancy, intrapartum intravenous ZDV at the onset and during labour, postpartum oral ZDV administered to the infant for 6 weeks (Connor *et al.* 1994)
#Bangkok protocol: antepartum oral ZDV initiated at 36 weeks gestation until delivery (Shaffer *et al.* 1999)

References:

1) (Sperling *et al.* 1998)
2) (Culnane *et al.* 1999)
3) (Chotpitayasunondh *et al.* 2001)

The Antiretroviral Pregnancy Registry (APR) in the USA is designed to monitor prenatal exposure to antiretroviral therapy and to assess the risk of birth defects. In 2004 the APR published their findings on over 3500 infants exposed to ART. Among 1391 first trimester exposures, the rate of birth defects was 2.7%, not significantly higher than the USA population surveillance rate (Watts *et al.* 2004).

1.6.2 Prematurity

The possibility of an association between *in utero* ART exposure and prematurity was first highlighted in a report from Switzerland in 1998. Of 30 infants exposed to PIs combined with other antiretroviral drugs, 10 were born prematurely (before 37 weeks gestation) (Lorenzi *et al.* 1998). Although the numbers were small in this study, the findings prompted a joint analysis between the ECS and the Swiss Mother + Child HIV Cohort. In nearly 4000 mother-child pairs, use of combination therapy in pregnancy was associated with a 2.5 times increased risk of prematurity compared with no therapy, adjusting for maternal HIV disease and drug use (European Collaborative Study and the Swiss Mother + Child HIV Cohort Study 2000). HAART use in pregnancy has been observed to be significantly associated with premature delivery in over 4000 infants born to HIV infected women in the UK and Ireland (Personal communication, P Tookey, 2006).

While European cohorts have reported an association between combination therapy, particularly HAART, and prematurity, this has not been observed in the USA. A meta-analysis including over 3000 mother-child pairs from seven cohorts did not find a statistically significant association between combination therapy and prematurity (Tuomala *et al.* 2002), and a more recent analysis from the WITS confirmed this (Tuomala *et al.* 2005). The disparity observed between cohorts in Europe and those in

the USA could be due to differences in the underlying population characteristics or methods used in data collection (Thorne *et al.* 2003).

1.6.3 Growth

Whether ART exposure has an adverse effect on growth has only been investigated in a small number of studies. Although findings to date have been reassuring, the analyses were only based on ZDV exposure (Sperling *et al.* 1998, Chotpitayasunondh *et al.* 2001) (Table 1.3).

1.6.4 Haematological parameters

Exposure to ZDV according to the PACTG 076 protocol has been associated with reversible anaemia in early life (Connor *et al.* 1994). Subsequent analyses of data on children enrolled in the PACTG 076 trial showed no differences between haematological parameters such as CD4 and CD8 lymphocytes at 18 months and three years of age (Sperling *et al.* 1998, Culnane *et al.* 1999) (Table 1.3). However, several more recent reports have suggested an association between ART exposure and haematological parameters in uninfected children. In the French Perinatal Cohort Study, over 4000 uninfected infants were followed up until 18 months of age and haematological variables were measured. As seen elsewhere, haemoglobin levels were transiently reduced in infants exposed to ZDV. In addition, platelets, neutrophils and lymphocytes were slightly lower in the ART-exposed infants than the unexposed; and combination therapy was associated with a larger decrease than monotherapy exposure, after adjusting for age, prematurity and maternal factors (Le Chenadec *et al.* 2003).

In the ECS, analyses of neutrophil counts up to eight years of age in just over 1500 uninfected children revealed that ART exposure (*in utero*, intrapartum or neonatal) was

significantly associated with a reduced count, after adjustment for year of birth, age and maternal factors (European Collaborative Study 2004b). A subsequent ECS analysis of over 1600 uninfected children, again up to eight years of age, showed that both duration and intensity of ART was associated with a reduced total lymphocyte count (European Collaborative Study 2005b). Lymphocytes and neutrophils are important components of the immune system. Whether the observed reduction associated with ART exposure has any clinical implications, such as increased susceptibility to viral and bacterial infections, is unknown.

1.6.5 Mitochondrial disorders and febrile seizures

As well as NRTIs having an affinity for reverse transcriptase, they are also substrates for DNA polymerase, the enzyme required for replication of mitochondrial DNA. In HIV infected adults, recognised adverse effects of NRTIs include myopathy, neuropathy and lactic acidaemia, complications associated with toxic effects on mitochondria (Morris and Carr 1999, Brinkman *et al.* 1998). Damage to the mitochondria of monkey fetuses has been observed after the maternal infusion of ZDV (Ewings *et al.* 2000); and damage in fetuses exposed to ZDV plus lamivudine has been found to be greater than when exposed to ZDV alone (Olivero *et al.* 2002).

In a report from France in 1999, Blanche *et al.* identified eight uninfected children with persistent mitochondrial dysfunction who had been exposed *in utero* and/or neonatally to ZDV or ZDV plus lamivudine, out of a total of 1754 ART-exposed children (Blanche *et al.* 1999). Two of the children presented with clinical symptoms and subsequently died aged 11 and 13 months of age. The other six children were identified through retrospective screening for mitochondrial symptoms. Five children in total, including the two who died, had neurological symptoms. Three children were symptom-free but were

identified due to abnormal biochemical test results. In a subsequent analysis from the French group, a predetermined algorithm was used for classifying unexplained symptoms compatible with mitochondrial dysfunction. The analysis included 4426 uninfected and indeterminate children, 2644 of whom had been exposed to ART (*in utero*, intrapartum or neonatal). Subsequent investigations were then carried out as appropriate. Further to the eight children identified in the previous review, four other children were found to have mitochondrial dysfunction. The 18-month incidence was 0.26% in ART-exposed children, compared with 0.01% in the general population (Barret *et al.* 2003). The French Perinatal Cohort Study also found exposure to ART was associated with febrile seizures in children younger than 18 months (Landreau-Mascaro *et al.* 2002), but this has not been observed elsewhere.

In response to the first French report, reviews of deaths of uninfected and indeterminate children born to HIV infected women in five cohorts in the USA were carried out. Of over 20 000 children in the cohorts, more than half had been exposed to NRTIs. A total of 223 children died. According to the classification system used, the cause of death for three indeterminate children was considered as being possibly related to a mitochondrial disorder. Two of these children had never been exposed to ART and the third child had not been exposed after birth. The rate of death due to sudden infant death syndrome (SIDS) (1.8/1000 live births) found in the five cohorts was not out of the normal range (The Perinatal Safety Review Working Group 2000, Dominguez *et al.* 2000, Bulterys *et al.* 2000).

Findings on the association between ART exposure and mitochondrial dysfunction are conflicting. The prevalence of mitochondrial dysfunction is rare in the general population, and probably linked to genetic factors (Thorne and Newell 2005). As

mitochondrial dysfunction is likely to be associated with a broad spectrum of clinical symptoms, its identification is particularly difficult. Neurological symptoms observed in cohorts of uninfected children born to HIV infected women may be due to other factors that affect this population, such as illicit drug exposure or prematurity.

1.6.6 Malignancies

As NRTIs become incorporated into host DNA, there is potential for long-term carcinogenic effects. In adult mice, ZDV is a weak carcinogen: Ayres *et al.* reported an increase in vaginal tumours after a lifetime exposure to the drug (Ayers *et al.* 1996). Findings from animal studies have also raised concerns over the potential for transplacental carcinogenic effects of ART. In adult mice exposed to high doses of ZDV, dose-dependent and significant increases in the incidence of lung, liver, skin and female reproductive organ tumours were observed in the offspring at one year of age (Olivero *et al.* 1997).

The relevance of animal data to humans is uncertain; however these studies show a theoretical risk of carcinogenicity. In an analysis of 234 uninfected children initially enrolled in the PACTG 076 trial (Connor *et al.* 1994) and who were subsequently followed up in the PACTG 219 study, no deaths or malignancies were observed in either the ZDV or placebo group after a median follow-up of four years (Culnane *et al.* 1999) (Table 1.3). Hanson *et al.* evaluated the short-term risk for tumours in 727 infants with *in utero* and/or neonatal ZDV exposure (Hanson *et al.* 1999). The infants were enrolled in the WITS and the PACTG 076/219 study, with mean length of follow-up of 14.5 months (743.7 person-years) and 38.3 months (366.9 person-years) respectively. No tumours were reported. Overall mortality was 2.3% (17/727), though no child had evidence of malignancy by autopsy or death certificate review.

Although reports from epidemiological studies have been reassuring to date, they have been limited in number and have only focused on ZDV exposure. Moreover, follow-up has only covered the first few years of childhood, and the findings do not preclude the possibility of malignancies occurring at later ages.

1.7 Conclusion

Many of the studies which have addressed ART exposure and the risk of adverse effects so far have been limited in scope; for example, most have only considered ZDV exposure. In addition, there has been limited work on the long-term effects of ART exposure, with most studies concentrating on the first few years of life (Sperling *et al.* 1998, Chotpitayasunondh *et al.* 2001, Culnane *et al.* 1999).

While national guidelines on treatment of HIV infected pregnant women recommend the long-term monitoring of uninfected children exposed to ART, practical ways of doing this are not laid out (Public Health Service Task Force 2005a). The benefits of ART in reducing rates of MTCT of HIV are great. However as concerns over safety have been raised, it is important to investigate further whether there is an association between ART exposure and adverse events in children; and what sort of mechanisms could be used to monitor any potential adverse side effects.

1.8 Aim and objectives of thesis

Aim

To explore the association between antiretroviral therapy (ART) exposure in fetal and/or early life and clinical outcomes in uninfected children born to HIV infected women in Europe.

Objectives

1) To describe the early social environment of uninfected children born to HIV infected women in a European cohort study.
2) To investigate the association between ART exposure, perinatal problems and subsequent adverse health outcomes in uninfected children.
3) To investigate the effect of ART exposure on growth in the first 18 months of life in uninfected children.
4) To explore the feasibility of monitoring death and cancer registration in children born to HIV infected women in England and Wales by matching perinatal data with national data on death and cancer held by the Office for National Statistics.
5) To assess the feasibility of a national clinic-based follow-up of uninfected children born to HIV infected women in the UK in order to monitor adverse health events that could be related to ART exposure in fetal and/or early life.
6) To assess parental and health professional perceptions of the acceptability of maintaining long-term contact with uninfected children.

Chapter 2 Data sources and methods

2.1 The European Collaborative Study

The European Collaborative Study (ECS) is an ongoing multi-centre cohort study. HIV infected women are enrolled in the ECS during pregnancy and their children are prospectively followed up according to standard protocols (European Collaborative Study 2001, European Collaborative Study 2003a) (Appendices 1 and 2). Aims of the ECS are to estimate the rate of and risk factors for mother-to-child transmission (MTCT) of HIV infection, to evaluate the benefits and potential risks of interventions to reduce MTCT and to assess the health of HIV infected pregnant women and their children. The ECS was established in 1985 and by the end of 2005 included 25 centres in 10 European countries. The ECS coordinating centre is based at the Institute of Child Health in London. Local ethics approval has been granted in all centres.

Informed consent is obtained before enrolment. Information collected at enrolment and during pregnancy includes maternal socio-demographic characteristics, antiretroviral therapy (ART) use, HIV-related laboratory tests, obstetric history, most likely mode of acquisition of HIV infection, and drug use on the basis of self-report and examination (European Collaborative Study 2004b).

Delivery and neonatal characteristics including gestational age, birth weight and the presence of congenital abnormalities are recorded (European Collaborative Study and the Swiss Mother + Child HIV Cohort Study 2000). At child follow-up assessments, information on laboratory tests, clinical findings and social care is collected according to standard laboratory and clinical protocols (European Collaborative Study 2003b, European Collaborative Study 2005c). In 13 paediatric centres, assessments are

scheduled at birth, at 3 and 6 weeks, at 3, 4.5, 6, 9, 12, 18 and 24 months, and then six-monthly for infected children and annually for uninfected children. In the remaining obstetric centres, follow-up is less intensive and usually only continues until the child's HIV status is determined.

Data collection forms (Appendix 2) are completed by clinicians in all centres. Forms are sent to the ECS coordinating centre by post or electronically. After verification and coding, data are entered onto the ECS database (Microsoft Access 2002). Routine data checking programmes are carried out.

Analyses

Analyses that were conducted for the purposes of this thesis, using ECS data on uninfected children and their mothers, are outlined in Table 2.1. Analyses of outcomes after three weeks of age were based on mother-child pairs from paediatric centres only. The description of ART exposure (Section 4.4) and the analysis of exposure to ART and early health outcomes (Section 4.5) were based on mother-child pairs from all centres.

Table 2.1 Analyses conducted using European Collaborative Study data

Analysis (year conducted)	ECS centres included in analysis	Mother-child pairs (n)	Age criteria of child	Chapter / section of thesis
1) Social environment (2002)	Paediatric	1667	Up to one year	3
2a) ART exposure (2001)	Obstetric & paediatric	2414	-	4.4
2b) Exposure to ART & early health outcomes (2001)	Obstetric & paediatric	2414	Up to three weeks	4.5
2c) Exposure to ART & longer-term health outcomes (2001)	Paediatric	1511	Up to age of last follow-up	4.6
3) Exposure to ART & growth (2003)	Paediatric	1912	Up to 18 months	5

ART, antiretroviral therapy

Data for the analyses were extracted from the ECS database. Inconsistencies in the data were identified through data checking processes and were investigated by consulting the original data collection forms or contacting the clinicians as appropriate.

Definitions

Infection status

A child was classed as uninfected if they were HIV antibody-negative at or after 18 months of age and no virus or antigen had ever been detected. If a child was aged less than 18 months and virological tests were negative on at least two occasions, the child was presumed uninfected (European Collaborative Study 2003a).

Gestational age

Gestational age was assessed by ultrasound and reported in completed weeks. A child was considered premature if gestational age was less than 37 weeks.

Maternal illicit drug use

Details on maternal illicit drug use (IDU) before and during pregnancy were based on self-report, recorded clinical presentation and presence of drug withdrawal symptoms in the neonate. Maternal IDU was categorised into "never", "past/timing unknown" and "current" to describe drug use in relation to the index pregnancy.

CD4 cell count

Maternal CD4 cell count, determined locally, has been routinely collected in the ECS since 1992. Where there were multiple measurements available for a pregnancy, the one closest to delivery was used in analyses. CD4 cell count in pregnancy was categorised into: <200, 200-499 and ≥ 500 cells/mm^3.

Antenatal ART exposure

Antenatal ART exposure was categorised into "none", "monotherapy" and "combination therapy" (double therapy and highly active antiretroviral therapy (HAART)). The most intensive drug therapy (in terms of number of drugs) that the mother was on during pregnancy was used in analyses.

2.2 The National Study of HIV in Pregnancy and Childhood

Surveillance of obstetric and paediatric HIV in the UK and Ireland is carried out through the National Study of HIV in Pregnancy and Childhood (NSHPC) also based at the Institute of Child Health (Ades *et al.* 1993, Tookey 2005b). The aims of the NSHPC are to monitor HIV infection in pregnant women and children, to monitor uptake of interventions to reduce MTCT and to explore progression of paediatric HIV infection (Nicoll *et al.* 1998, Gibb *et al.* 2003). Obstetric data are used for alignment with results from the unlinked anonymous (UA) surveys to estimate detection rates for HIV in pregnancy (The UK Collaborative Group for HIV and STI Surveillance 2005). Paediatric data are included in national quarterly surveillance reports, and in the Survey of Prevalent HIV Infections Diagnosed (SOPHID) which is used for service planning and resource allocation (The UK Collaborative Group for HIV and STI Surveillance 2005).

The core surveillance mechanisms are two parallel reporting schemes, both of which are anonymous, active, confidential and voluntary (Ades *et al.* 1993). Children with HIV infection and children born to HIV infected women are reported to the NSHPC either through the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health (RCPCH) (British Paediatric Surveillance Unit 2005) or directly (Figure 2.1). Respondents provide information on HIV-related laboratory investigations, perinatal details, vital status, ART exposure, maternal risk group and

maternal demographic characteristics (Appendix 3.3). Reports are followed up to establish infection status (Appendices 3.3 and 3.4). Once reported children are confirmed uninfected, no further information is requested for surveillance purposes. Definitions of infection status used in the NSHPC are outlined in Appendix 3.3.

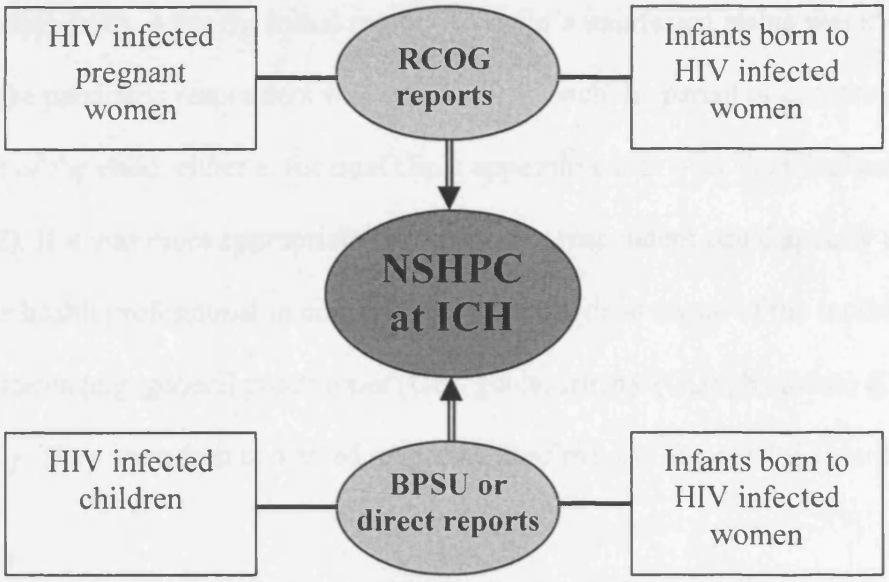
In the second reporting scheme, pregnancies in HIV infected women are reported through a system run by the NSHPC under the auspices of the Royal College of Obstetricians and Gynaecologists (RCOG) (Figure 2.1). Respondents provide information on maternal demographic characteristics, risk group, ART use and pregnancy outcome (Appendices 3.1 and 3.2).

Live births reported through the obstetric scheme are linked with paediatric reports using demographic information, in order to combine data on the mother and child, and to avoid double counting of a birth (Ades *et al.* 1993). Laboratory reports are also made to the NSHPC and are linked with paediatric and obstetric reports. The paediatric and obstetric reporting schemes were established in 1986 and 1989 respectively. The majority of infants are reported through both schemes.

Data collection forms are processed, and inconsistencies in the data are clarified with respondents. Data are entered onto the NSHPC database (Microsoft Access 2002) and routine data checking programmes are carried out. The NSHPC is national anonymised surveillance and there is no enrolment; consent for notification of reports is not requested. Case identifiers include date and place of birth, hospital number, initials, truncated postcode of residence (postcode with the last letter deleted e.g. A12 3BC truncated to A12 3B) and National Health Service (NHS) number where available (see Appendix 3). The NSHPC was most recently reviewed and approved by the London

Multi-centre Research Ethics Committee in 2004 (ref 04/2/009). Overlap between the ECS and NSHPC is very limited and does not affect the analyses presented in this thesis.

Figure 2.1 The National Study of HIV in Pregnancy and Childhood: obstetric and paediatric surveillance



RCOG, Royal College of Obstetricians and Gynaecologists; BPSU, British Paediatric Surveillance Unit; NSHPC, National Study of HIV in Pregnancy and Childhood; ICH, Institute of Child Health

2.3 Follow up of uninfected children born to HIV infected women: the CHART study

The CHART study, carried out between 2002 and 2005, was a consented annual clinic-based follow-up of uninfected children born to HIV infected women in the UK and reported to the NSHPC. The aims of the CHART study were to explore the feasibility of clinic-based follow-up of uninfected children on a national basis to monitor adverse health events that could be related to ART exposure in fetal and/or early life; and to investigate adverse health events reported for children enrolled in the study, with respect to ART exposure.

Study protocol

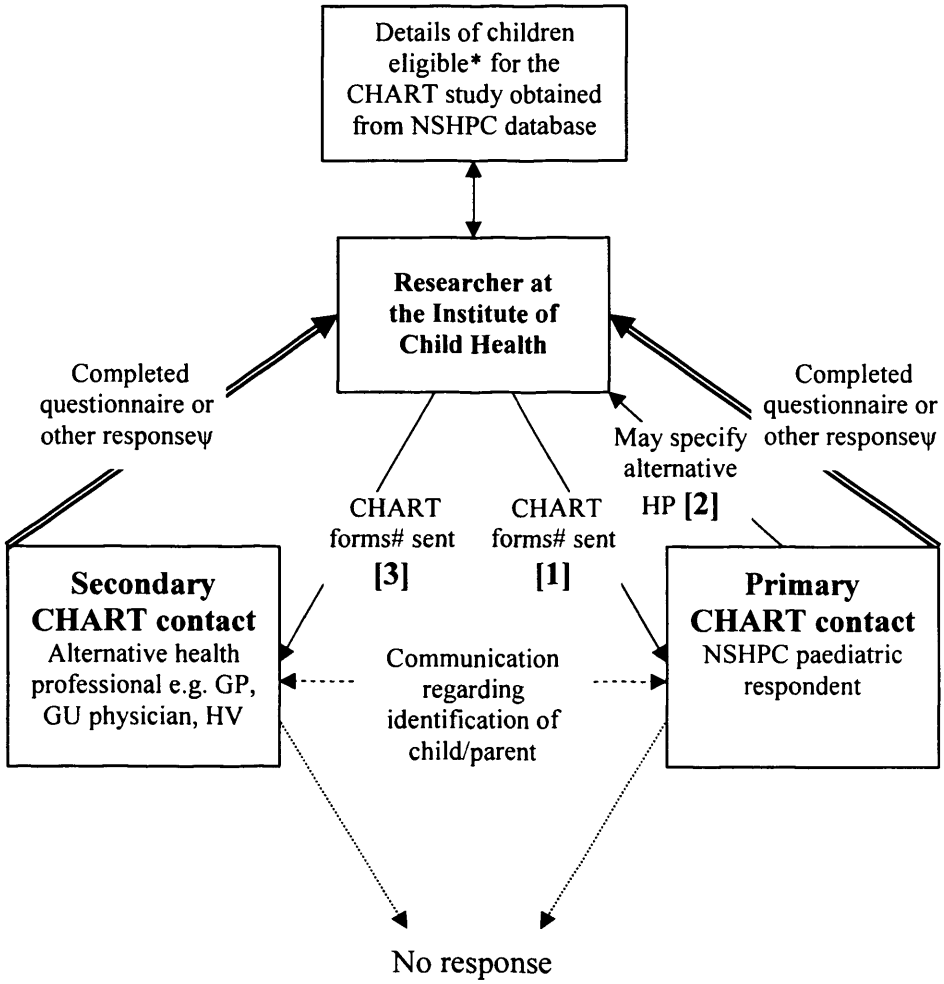
The CHART study was dependent on the NSHPC for the identification of uninfected children, as well as for prospectively collected perinatal, demographic and ART exposure information. As reports to the NSHPC do not include names or contact details of cases, enrolment and data collection in the CHART study was reliant on a network of health professionals. After the initial report of a child's uninfected status was made to the NSHPC, the paediatric respondent was asked to approach the parent or carer regarding enrolment of the child, either at the next clinic appointment or over the telephone ([1] on Figure 2.2). If it was more appropriate, the paediatric respondent could specify an alternative health professional in contact with the family and aware of the mother's HIV infection status (e.g. general practitioner (GP), genitourinary (GU) physician) ([2] on Figure 2.2). They were then contacted regarding enrolment of the child ([3] on Figure 2.2).

Consent was sought from the parent or carer, and a questionnaire was completed by the health professional in consultation with them (Appendix 6.2). The consent form (Appendix 6.3) and a copy of the questionnaire were kept in the clinic; confirmation of consent (Appendix 6.1) and a copy of the questionnaire were returned to the researcher at the Institute of Child Health. Subsequent questionnaires were then sent to appropriate health professionals a year after the previous one had been completed. If the child could not be enrolled for any reason (e.g. they had left the UK, were lost to follow-up, parent or carer had declined), this was recorded on the follow-up status form (Appendix 6.1).

The study protocol was flexible so that every attempt was made to ensure that enrolment and data collection was done in the most convenient way for both the health professional

and the parent or carer. Additional clinic appointments were not requested. The eligibility criteria for the CHART study are outlined in Chapter 7.

Figure 2.2 The CHART study protocol



Notes
HP, health professional; GP, general practitioner; GU, genitourinary; HV, health visitor; NSHPC, National Study of HIV in Pregnancy and Childhood.
* eligibility criteria are outlined in Chapter 7
ψ other responses: parent/carer declined, not possible to enrol child (e.g. lost to follow-up, left UK, inappropriate to contact family).
CHART forms: information sheets, questionnaire, follow-up status form.

Information sheets

Information sheets were provided for both the health professional and the parent or carer. They included details on what was involved in the study, guidance on completing the questionnaire and contact details of the researcher (Appendices 6.3 and 6.4).

Questionnaire

A standard summary of routinely available information on the child's general health and development was collected on the CHART study questionnaire (see Appendix 6.2). No investigations additional to routine clinical care were requested. The questionnaire, though completed by the health professional, was directed to the parent or carer of the child. It was designed to cause minimal inconvenience to the health professional and family, and to act as a filter to identify children with any major health problems. Ideally the questionnaire was completed in the presence of the child and their parent or carer, but if necessary the health professional could complete the questionnaire in the absence of the child, or over the telephone.

Data management

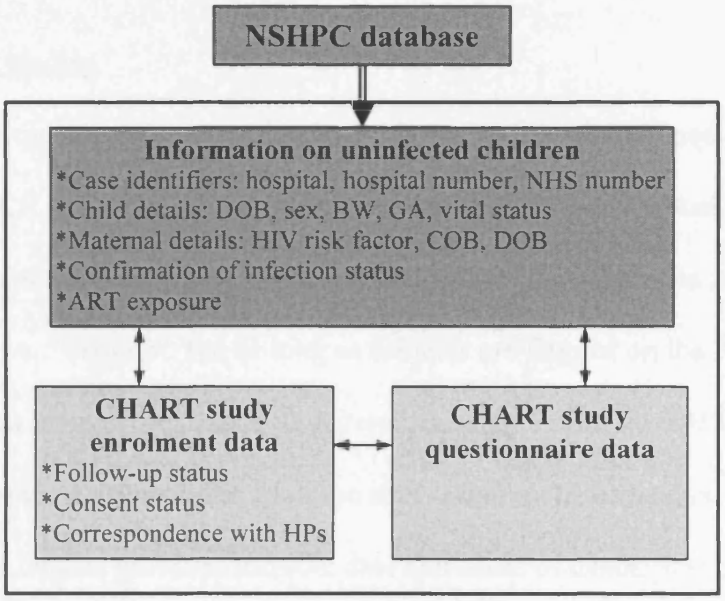
A Microsoft Access 2002 database was established which was used both for study management and data storage. This combined prospectively collected data from the NSHPC database, with the CHART study enrolment and questionnaire data (see Figure 2.3).

Univariable comparisons for categorical variables were tested with χ^2 tests or χ^2 tests for linear trend. Data analysis was carried out using SAS statistical software (version 9.1, SAS Institute, Cary, North Carolina, USA).

Ethics approval

The CHART study was reviewed and approved by the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Local Research Ethics Committee in 2001 for the period 2001-2006. Due to changing requirements regarding ethics approval, the CHART study was reviewed and approved by the London Multi-centre Research Ethics Committee in 2004 for the period 2004-2006 (ref 04/MRE02/47).

Figure 2.3 Data management in the CHART study



HP, health professional; NSHPC, National Study of HIV in Pregnancy and Childhood; DOB, date of birth; COB, country of birth; BW, birth weight; GA, gestational age; NHS, National Health Service

2.4 The Office for National Statistics flagging study

National Health Service Central Register

The National Health Service Central Register (NHSCR) is the central record of National Health Service (NHS) patients registered in England and Wales, and is administered by the Office for National Statistics (ONS). The NHSCR database, developed in 1991, holds

a unique record for every patient who was alive and registered in 1991, plus anyone who has registered since; and all births in England and Wales since 1991 (Botting *et al.* 1995). Recorded data include:

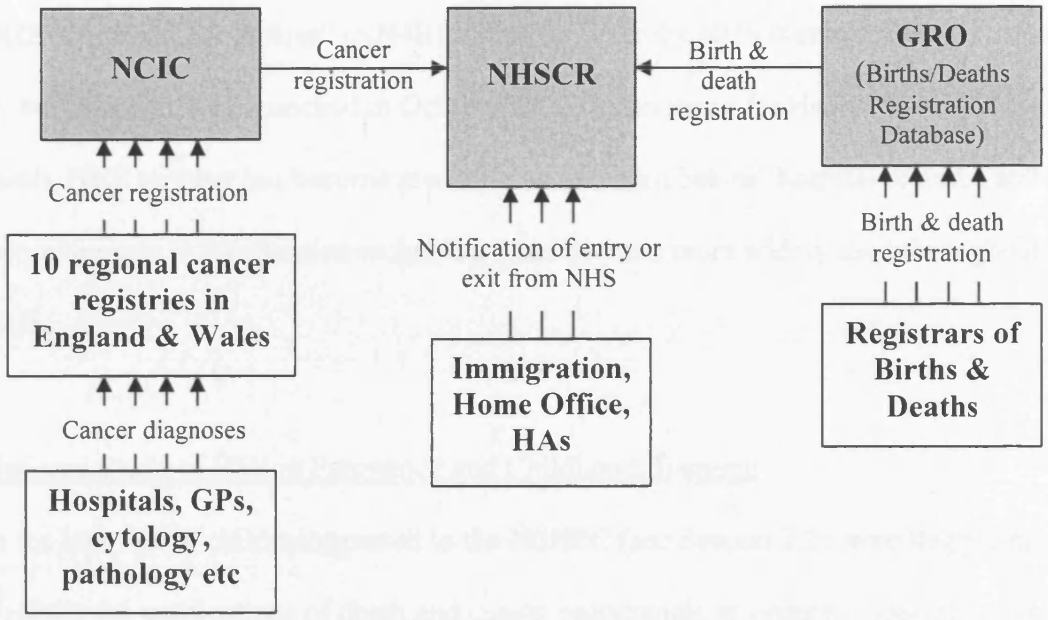
- NHS number, name, sex, date of birth
- health authority where the patient is registered with a GP
- if applicable: death registration, cancer registration, entry or exit from the NHS (e.g. known to have left the UK, or gone into prison, a psychiatric hospital or the care of the armed forces)

Flagging studies

With appropriate approval and safeguards on confidentiality, medical researchers can use the NHSCR to monitor death and cancer registration in individual subjects in their study. Once subjects have been identified on the NHSCR, their records are marked with a study number, i.e. "flagged". For as long as subjects are flagged on the NHSCR, if any of them die, have a diagnosis of cancer registered, or enter or exit the NHS (have an "event"), then a designated researcher from the study receives a notification from ONS (Botting *et al.* 1995). Details provided include: date and cause of death; year of diagnosis, site and type of cancer (Greenberg and Coleman 2000). Retrospective events are notified. Events are reported to the NHSCR from various sources (see Figure 2.4):

- Death registration is mandatory and is reported from the General Register Office (GRO) at ONS.
- Details of cancer diagnoses are reported from regional cancer registries via the National Cancer Intelligence Centre (NCIC) at ONS. Reporting has been mandatory since 1993 (Office for National Statistics 2005).
- Entry or exit from the NHS can be reported from sources such as Immigration, the Home Office and health authorities.

Figure 2.4 The National Health Service Central Register and event reporting



Notes: NCIC, National Cancer Intelligence Centre; GRO, General Register Office; HA, health authority; NHSCR, National Health Service Central Register; GP, general practitioner; NHS, National Health Service

Identification of subjects on the NHSCR is determined by whether date of birth, NHS number (see below) and name are available to the researchers. If subjects cannot be traced directly on the NHSCR, but appropriate information on them is available, e.g. date of birth, sex and mother's date of birth, the Births/Deaths Registration Database (BDRD) at the GRO can be searched to identify the birth registration records of the subjects. Details obtained from these can then be used to identify the records on the NHSCR, which can then be flagged. Fees for flagging work charged by ONS are based on the number of subjects attempted to flag and how they are identified; and a fee is charged each time an event is notified.

National Health Service number

The NHS number is a unique identifier given to babies born in England and Wales, and to patients registered with the NHS. Up until 2002, NHS number was allocated to a baby

at the time of civil registration, which could have been up to six weeks after birth. The NHS "Numbers for Babies" (NN4B) initiative, whereby NHS number is issued at birth by the midwife, was launched in October 2002 (Connecting for Health 2006b). As a result, NHS number has become available on newborn babies' hospital records; and with improvements in information technology, has become more widely used throughout the NHS.

National Study of HIV in Pregnancy and Childhood: flagging

In the late 1990s, children reported to the NSHPC (see Section 2.2) were flagged on the NHSCR for notifications of death and cancer registration, in order to monitor possible long-term adverse outcomes in children exposed to ART. The BDRD was manually searched to identify the birth registration records of the children. A total of 329 children born in England and Wales between 1996 and 1999 were flagged in this way. However, progress was slow because of the manual approach to identifying birth registration records and because of the then limited availability of NHS number in the NSHPC. After the implementation of the NN4B initiative however, the proportion of reports to the NSHPC for which NHS number was provided increased.

In 2005 a revised protocol was developed for flagging children reported to the NSHPC on the NHSCR, through an automatic matching procedure. Details on the protocol are provided in Chapter 6.

Flagging studies which were underway in 2002 have support under Section 60 of the Health and Social Care Act 2001 from the Patient Information Advisory Group (PIAG) (ref PIAG 4-07(h)/2002). The ONS flagging study was most recently reviewed and

approved by the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Local Research Ethics Committee in 2001 for the period 2001-2006.

2.5 Parent and carer survey

To obtain views of parents and carers on the importance and acceptability of the long-term follow-up of uninfected children, a cross-sectional survey was carried out in 2004/5. Parents and carers were invited to participate if they cared for at least one uninfected child born in the UK to an HIV infected woman who took ART during pregnancy. The survey method used was a self-completed anonymous questionnaire (Appendix 11).

The survey was conducted in 12 paediatric and two GU clinics in 12 hospitals in England, Scotland and Wales (Appendix 9). Hospitals were selected on the basis of the number of reports of uninfected children made to the NSHPC, and also to give a geographically representative sample (Table 2.2). The survey was reviewed and approved by the London Multi-centre Research Ethics Committee (ref 04/MRE02/48).

Researcher clinics

The researcher visited five paediatric clinics and one GU clinic in London on 33 occasions to invite potential respondents to participate in the survey (see Table 8.1). Children booked for the paediatric clinics were generally attending for their 3, 12 or 18 month blood tests. The researcher liaised with clinic staff so only parents and carers who met the inclusion criteria were approached. Discussion between the researcher and the parent or carer took place in a private consultation room; and generally questionnaires were completed there, though they could be completed at home and returned by post. The researcher consulted with clinic staff to ensure that potential respondents were only

approached once. The number of children booked for the clinic and number attended were also recorded each time the researcher visited a paediatric clinic. Data collection took place between October 2004 and June 2005.

Table 2.2 Uninfected children born to HIV infected women in the UK reported to the NSHPC and the number of hospitals included in the parent and carer survey

Geographical region	Uninfected children reported to the NSHPC* n (%)	Hospitals in the survey (n)	Uninfected children reported to the NSHPC* from hospitals in the survey n (%)
England#			
London	672 (62)	6	351 (88)
South	118 (11)	2	25 (6)
North	82 (8)	1	3 (1)
Midlands & the East	158 (15)	1	7 (2)
Wales	8 (1)	1	4 (1)
Scotland	40 (4)	1	8 (2)
Northern Ireland	1 (<1)	-	-
Total	**1079**	**12**	**398**

NSHPC, National Study of HIV in Pregnancy and Childhood
*born since 2001 and reported to the NSHPC by April 2004
#by Strategic Health Authority region

Non-researcher clinics

The clinic caseload was smaller in the survey hospitals outside London (Table 2.2) and clinic staff agreed they could coordinate recruitment. Potential respondents were invited in clinic to participate, or if the health professional thought it appropriate, they were sent the survey material (see Table 8.2). Questionnaires were returned directly to the researcher in a prepaid envelope. Staff in one paediatric clinic and one GU clinic in London were able to manage recruitment.

Other respondents

Potential respondents were also invited to participate by a member of staff at Positively Women, a support group for HIV-affected women (www.positivelywomen.org.uk), and through an advert in Positive Nation, a magazine published by the UK Coalition of People Living with HIV and AIDS (www.positivenation.co.uk). These questionnaires were returned directly to the researcher.

Survey information sheet and questionnaire

An information sheet was provided for all potential respondents to explain why the survey was being conducted and to provide assurance that it was anonymous and voluntary (Appendix 10). The questionnaire was piloted with the assistance of Positively Women, and comments on drafts of the information sheet and questionnaire were obtained from colleagues at the Institute of Child Health. The questionnaire included general questions about the respondent's family and their contact with health services. Several possible long-term follow-up options were described, and respondents' views on them were sought. Further details are provided in Section 8.5. Only limited personal and demographic information was requested on the questionnaire, and at the end there was a section for comments (Appendix 11). The survey material was translated into French, a common alternative language for HIV-affected families in the UK.

Statistical analysis

A database for survey management and data entry was designed in Microsoft Access 2002. Data analysis was conducted using SAS statistical software (version 9.1, SAS Institute, Cary, North Carolina, USA). Univariable comparisons of categorical variables were tested with χ^2 tests, and comparisons of means were tested with t tests.

2.6 Health professional survey

A questionnaire survey was conducted with health professionals to obtain information on their experiences with the CHART study, and their views on approaches to long-term follow-up of ART-exposed uninfected children. Health professionals were asked to take part in the survey if they were the main NSHPC paediatric respondent in a hospital where:

- 10 or more uninfected children born 2001-April 2004 had been reported to the NSHPC by April 2005, regardless of enrolment in the CHART study (35 hospitals)
- less than 10 uninfected children born 2001-April 2004 had been reported to the NSHPC by April 2005, and at least two children had been enrolled in the CHART study (11 hospitals)

A distinction was made between hospitals with 10 or more reported children and those with less than 10 reported children, as the majority of uninfected children reported in the specified time period were from the former (1340/1760, 76%) and the latter consisted of 125 hospitals.

The questionnaire consisted of structured questions and there was space at the end for additional comments (Appendix 7). Respondents were asked about clinic practice in their hospital regarding uninfected children, their involvement in the CHART study and issues they felt could have affected study enrolment. Four long-term follow-up scenarios for uninfected children were outlined in the questionnaire, and respondents were asked which they found acceptable and if there were any they strongly objected to. The scenarios and questions corresponded to the parent and carer survey questionnaire (see Sections 2.5 and 8.5).

The questionnaire and a covering letter explaining the aims of survey were sent to 46 NSHPC paediatric respondents in June 2005 to coincide with the end of the data collection for the CHART study. Those who had not responded after one month were sent a reminder email with another copy of the questionnaire. Data collection ceased in August 2005. A database for survey management and data entry was designed in Microsoft Access 2002. Data analysis was conducted using SAS statistical software (version 9.1, SAS Institute, Cary, North Carolina, USA). Univariable comparisons of categorical variables were tested with χ^2 tests.

Chapter 3 Social environment of uninfected children

"....I find it crucial to keep our family health care as 'normal' as possible - less explaining, and I think less stigmatised."

[Mother of one child (aged 6 years)]

3.1 Introduction

Morbidity and mortality within HIV-affected families could result in children requiring social care from non-parental sources (Blanche *et al.* 1996, Paul *et al.* 2005). Families may also have immigration, drug or financial problems (Rajamanoharan *et al.* 2004, Mok *et al.* 1996, Schrooten *et al.* 2002). These issues, together with concerns over confidentiality and the stigma of HIV, may affect families' access to health and social services. In order to provide a general background against which to assess possible adverse effects of antiretroviral therapy (ART) exposure and mechanisms to monitor them, the early social environment and morbidity of uninfected children in the European Collaborative Study (ECS) are described is this chapter.

3.2 Methods

The methods of the ECS are described in Section 2.1. Univariable comparisons for categorical variables were tested with χ^2 tests or χ^2 tests for linear trend. Univariable and multivariable logistic regression was used to obtain odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI) (SAS statistical software, version 8.02, SAS Institute, Cary, North Carolina, USA). General definitions are provided in Section 2.1, but those specific to this chapter are described here.

Mode of acquisition of maternal HIV infection

Reported mode of acquisition of maternal HIV infection was categorised to capture the broad social circumstances of the woman around the time of enrolment in the ECS, and therefore the child's early environment (Mok *et al.* 1996, Nostlinger *et al.* 2004, Anderson and Doyal 2004):

- *Intravenous drug use-related:* woman was a past or current intravenous drug user and/or woman had a sexual partner with a history of intravenous drug use

- *From an HIV high-prevalence country:* woman was from a country with a high prevalence of HIV infection e.g. sub-Saharan African countries, Thailand (UNAIDS/WHO 2005) (most likely heterosexual contact)
- *Other heterosexual contact:* woman acquired HIV infection heterosexually but was not reported to be from an HIV high-prevalence country or to have had a sexual partner with a history of intravenous drug use
- *Blood transfusion recipient:* woman acquired HIV infection through a blood transfusion
- *Not stated:* risk factor not stated by reporting clinician (most likely heterosexual contact)

Maternal HIV disease

Disease staging at enrolment was categorised into "AIDS" (CDC stages 4C1 and 4D) and "non-AIDS" (Centers for Disease Control and Prevention 1992).

Social care

The type of social care that a child had at the time of each follow-up assessment was categorised into "parental" if they were living with one or both of their natural parents and "alternative" if they were living with other relatives, a foster or adoptive parent, or in a hospital or institution (European Collaborative Study 1998).

Child morbidity

Reported morbidity information at each follow-up assessment, relating to infective episodes requiring medical attention were categorised into "moderate/severe" (diarrhoea, unexplained fever, sepsis, meningitis, urinary tract infection, pneumonia and other serious bacterial infection) and "mild" (lymphadenopathy, hepatomegaly, splenomegaly,

dermatitis, parotitis, upper respiratory infection, sinusitis, otitis media, oral candida). Mild episodes were grouped with no reported episodes in this analysis. A hospital admission was defined as a stay in hospital for at least one night after the delivery-associated routine postnatal stay.

3.3 Socio-demographic characteristics of mother-child pairs

By November 2002, 1667 uninfected children (51.5% male) born to 1494 HIV infected women had been enrolled in ECS paediatric centres. Among these children were 157 sets of siblings, including 25 sets of twins and one set of triplets. Fourteen uninfected children had an HIV infected older sibling and three had an HIV infected twin also enrolled in the ECS. This analysis included 66 children born less than one year before the time of analysis. Total length of follow-up in the first year of life for the 1667 uninfected children was 1475 child-years.

Socio-demographic characteristics for the 1667 mother-child pairs are shown in Table 3.1. Overall median maternal age was 27.5 years (range 14.0-44.9) and this had increased from 23.2 years for children born in 1985 to 28.4 years in 2002. For children born to white women, median maternal age was slightly lower (26.9 years) than for black (28.9 years) and other ethnicities (28.2 years).

The proportion of infants born to black women (the majority from sub-Saharan Africa) increased from 5% (10/215) in 1985-1987 to 46% (136/296) in 2000-2002 (χ^2_{trend}, 208.86, $p<0.001$); the proportion born to white women decreased from 93% (200/215) to 47% (140/296) (χ^2_{trend}, 235.54, $p<0.001$). Few infants were born to women of other ethnicities, though the proportion increased gradually over time from 2% (5/215) in 1985-1987 to 7% (20/296) in 2000-2002 (χ^2_{trend}, 10.91, $p<0.001$). These trends were

observed both in southern European centres (Italy and Spain) and northern European centres (Germany, UK, The Netherlands, Sweden, Belgium and Denmark).

Table 3.1 Socio-demographic characteristics of mother-child pairs

	n (%)
Child year of birth (n=1664)	
1985-1990	580 (35)
1991-1996	460 (28)
1997-2002	624 (38)
Child country of birth (n=1667)	
Belgium	291 (17)
Denmark	30 (2)
Germany	229 (14)
Italy	386 (23)
Spain	366 (22)
Sweden	178 (11)
The Netherlands	81 (5)
UK	106 (6)
Maternal ethnicity (n=1603)	
White	1064 (66)
Black	449 (28)
Other	90 (6)
Maternal area of birth (n=1559)	
Europe	1044 (67)
Sub-Saharan Africa	431 (28)
The Americas	36 (2)
Asia	28 (2)
North Africa & Middle East	20 (1)
Maternal age (n=1525)	
<25 years	476 (31)
25-29 years	552 (36)
>29 years	497 (33)
Maternal previous live births (n=1514)	
0	776 (51)
1	432 (29)
2	169 (11)
3	80 (5)
4 or more	57 (4)

Overall, of children born in southern European centres, more had a mother who was white (650/731, 89%) than black (50/731, 7%), whereas for those born in northern European centres, there was little difference: 47% (414/872) and 46% (399/872) respectively.

A total of 568 (568/1559, 36%) children were born to women who themselves had been born abroad. Of those born abroad, most were from sub-Saharan African countries (431/568, 76%), particularly Democratic Republic of the Congo (Zaire), Uganda, Ghana and Rwanda.

Mode of acquisition of maternal HIV infection

The most commonly reported mode of acquisition of maternal HIV infection was intravenous drug use-related (Table 3.2). A total of 728 children (728/1667, 44%) had mothers who were past or current intravenous drug users, and just over half of these (n=389) had mothers who had a sexual partner with a history of intravenous drug use. A further 160 children (160/1667, 10%) had mothers who had a sexual partner with a history of intravenous drug use, though they were not reported to have been users themselves. There was little overlap between intravenous drug use-related acquisition and other risk factors for HIV infection, though prostitution or many sexual partners had been reported for the mothers of 32 children; and another 33 children were born to mothers who had high-risk sexual partners not known to be intravenous drug users: haemophiliac (2), bisexual (2), prisoner (1), known HIV infected (2), from an HIV high-prevalence country (1), unspecified (25).

A quarter of children (434/1667, 26%) were born to women from an HIV high-prevalence country, who were most likely to have acquired their HIV infection

heterosexually; and in 326 cases, a sexual partner from an HIV high-prevalence country was also reported as a risk factor. The majority of these 434 children were born to mothers who were black and from sub-Saharan Africa (392/434, 90%).

Table 3.2 Maternal HIV-related characteristics of mother-child pairs

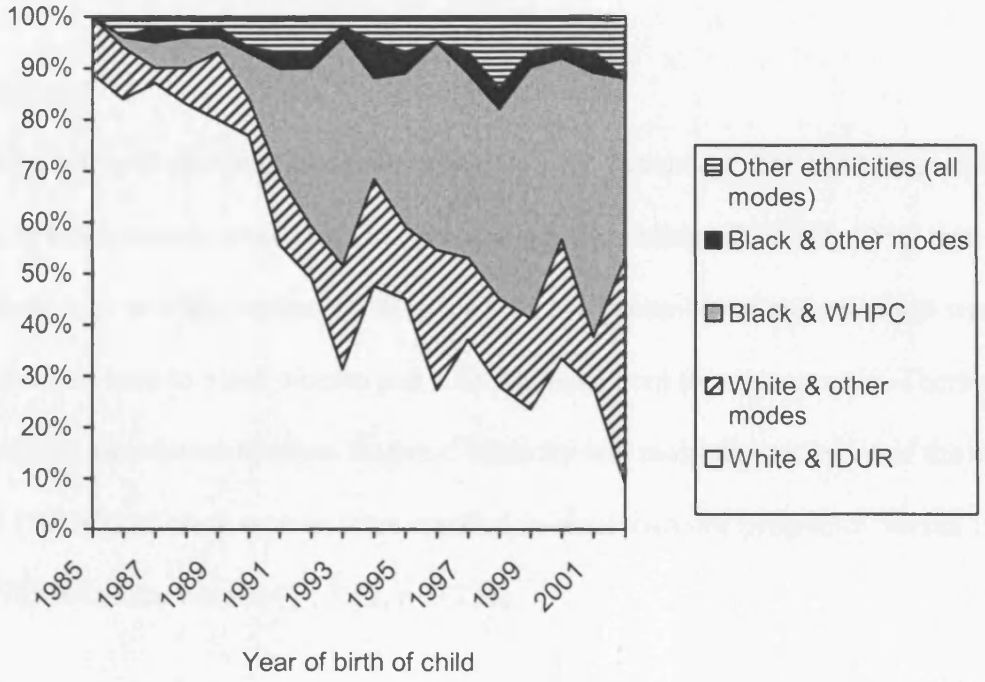
	n (%)
Mode of acquisition of HIV infection (n=1667)	
Intravenous drug use-related*	888 (53)
From an HIV high-prevalence country	434 (26)
Other heterosexual contact§	188 (11)
Blood transfusion recipient	23 (1)
Not stated	134 (8)
Clinical status at enrolment (n=1667)	
Non-AIDS	1603 (96)
AIDS	64 (4)
Antenatal antiretroviral therapy (n=1667)	
No	975 (58)
Yes	692 (42)

* Includes 5 whose mother was from an HIV high-prevalence country
§ Rape, prostitution/many sexual partners; or a sexual partner who was: haemophiliac, blood transfusion recipient, bisexual, prisoner, known HIV infected, from an HIV high-prevalence country, of an unspecified risk factor.

A total of 11% (188/1667) of children were born to women who acquired HIV infection heterosexually but who were not reported to be either from an HIV high-prevalence country or to have had sexual contact with an intravenous drug user. In these cases, the reported mode of acquisition was rape (2), prostitution or many sexual partners (16); or a sexual partner who was haemophiliac (6), a blood transfusion recipient (1), bisexual (10), a prisoner (2), known HIV infected (37), from an HIV high-prevalence country (38) or with an unspecified risk factor (76). Eight percent (134/1667) of children were born to women where a risk factor had not been stated, though it is likely that these women acquired their infection heterosexually (Table 3.2).

Over the study period, intravenous drug use-related HIV infection decreased from 87% (409/470) in 1985-1989 to 27% (116/436) in 1999-2002, and HIV high-prevalence country acquired infection increased from 4% (20/470) to 45% (197/436) (Figure 3.1).

Figure 3.1 Trends in maternal ethnicity and mode of acquisition of HIV infection for mother-child pairs



IDUR, intravenous drug use-related; WHPC, woman from an HIV high-prevalence country
Uninfected children enrolled in paediatric centres by year of birth: 1985-1987 n=215, 1988-1990 n=359, 1991-1993 n=193, 1994-1996 n=243, 1997-1999 n=296, 2000-2002 n=296.

Maternal AIDS and antenatal ART use

Only 4% (n=64) of infants were born to mothers who had progressed to AIDS by the time of enrolment in the ECS. Of children born after 1994, 83% (656/788) were born to mothers who had taken ART during pregnancy, which was in line with their increasing use either to delay HIV disease progression and/or to prevent mother-to-child transmission (Connor *et al.* 1994, Kirk *et al.* 1998, European Collaborative Study 2005c) (Table 3.2).

Maternal illicit drug use (IDU)

Infants born earlier in the study period were more likely to have been born to women who used illicit drugs during pregnancy than those born later: 36% (167/468) of infants born before 1990 versus 10% (114/1121) of infants born from 1990 onwards (χ^2, 147.65, $p<0.001$), and this was observed for infants both in northern and southern European centres.

Family size

Using number of previous live births as a proxy for current number of siblings, children born to black women were more likely to have older siblings (278/441, 63%) than children born to white women (400/967, 41%). Mean number of older siblings was 1.83 for children born to black women and 1.68 for those born to white women. There was no significant association between maternal ethnicity and multiple enrolment of the mother: 13% (50/397) of black women were enrolled in more than one pregnancy versus 10% (99/955) of white women (χ^2, 1.42, $p=0.233$).

3.4 Social care in the first year of life

Information on social care in the first year of life was available for 1652 (99%) of the 1667 children enrolled in ECS paediatric centres. Of the remaining 15 children, all were born to mothers not living with a partner at the time of enrolment.

By their last assessment in the first year of life, most children (1465/1652, 89%) had lived with one or both of their parents since birth. A total of 122 (7%) children had been in both parental and alternative care. Generally children were only cared for in one type of alternative care (Table 3.3), though they may have been moved several times between this care setting and their parents. At their last assessment, 73 of the 122 children (60%)

were in parental care. Four percent of children (n=65) had always lived in alternative care (Table 3.3). Of the 187 children who had been in alternative care, half had lived with other relatives (94/187, 50%) and these were generally grandparents; 44% (82/187) had lived in a foster or adoptive family setting and 19% (35/187) in a hospital or institution.

Table 3.3 Type of alternative care that children had in their first year of life

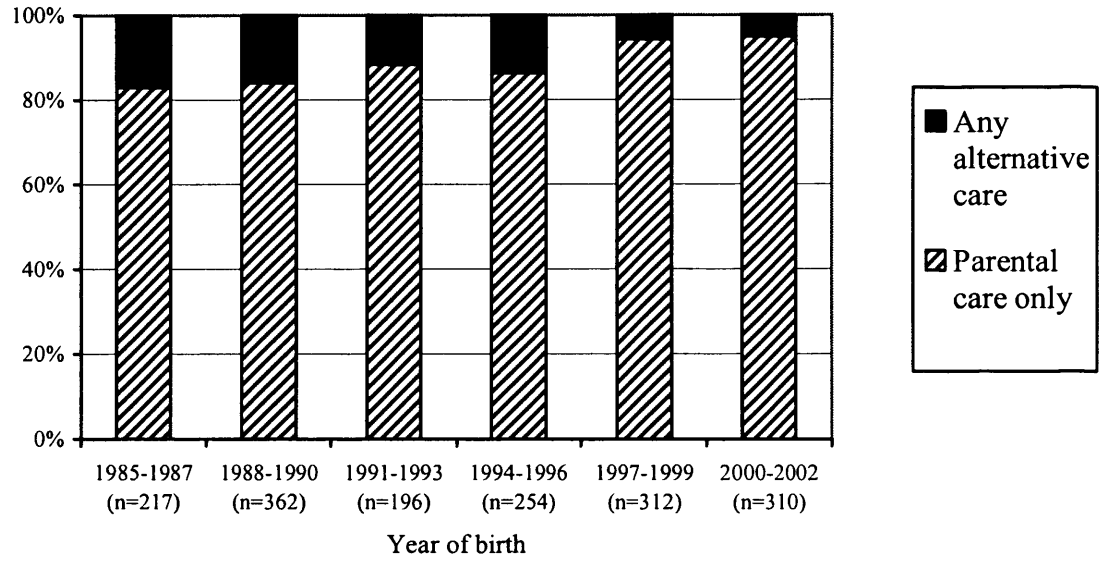
Type of care	Children who spent some time in alternative care n (%)	Children who were always in alternative care n (%)
Non-parental relative only	55 (45)	19 (29)
Fostered only	40 (33)	20 (31)
Adopted only	2 (2)	3 (5)
Hospital only	4 (3)	8 (12)
Institution only	9 (7)	2 (3)
More than one type of alternative care*	12 (10)	13 (20)
Total	**122 (100)**	**65 (100)**

*non-parental relative, adoptive or foster parent, hospital or institution

The proportion of children who had been in alternative care in the first year of life decreased over the study period from 17% (37/217) in 1985-1987 to 5% (16/310) in 2000-2002 (χ^2_{trend}, 33.07, $p<0.001$) (Figure 3.2).

Children born to women who were reported to have used illicit drugs during pregnancy were more likely to have spent time in alternative care than children whose mothers had no reported drug use, after adjusting for maternal ethnicity, age and clinical status (AOR=14.54, 95% CI: 7.72-27.40, $p<0.001$). Maternal ethnicity and clinical status were not associated with alternative care placement, after adjusting for maternal IDU, age and clinical status or ethnicity respectively.

Figure 3.2 Type of social care by year of birth of child



3.5 Morbidity and hospitalisation in the first year of life

Infectious disease morbidity

Sufficient information to enable categorisation of infectious disease morbidity in the first year of life was available for 1617 (97%) of the 1667 uninfected children. Of the remaining 50 children, 52% (26/50) were born to women who had intravenous drug use-related HIV infection and nearly two thirds were born to white women (n=32).

A total of 135 (135/1617, 8%) infants experienced at least one moderate/severe infective episode requiring medical attention in the first year of life. Of these, 92 infants had at least one episode of diarrhoea, 47 had at least one episode of a serious bacterial infection (most commonly sepsis (10), pneumonia (12), urinary tract infection (8), meningitis (6)); and 13 had an unexplained fever. There were 183 episodes in total and 36 children had more than one episode.

The proportion of children who had a moderate/severe infective episode decreased over the study period: from 11% (61/557) of children born in 1985-1990 to 7% (44/614) in 1997-2002 (χ^2_{trend}, 5.29, p=0.021). Although nearly half of the episodes of bacterial infection (24/53, 45%) occurred during the first three months of life, no specific pattern was observed for episodes of diarrhoea or fever. There were four episodes of bacterial infection, one of fever and eight of diarrhoea per 100 child-years of follow-up. There was little correlation between recorded socio-demographic and child characteristics, and risk of the infant having a moderate/severe infective episode requiring medical attention in the first year of life.

Hospitalisation

Hospitalisation for any reason in the first year of life in uninfected children remained relatively stable over the study period: 264 admissions per 1000 child-years of follow-up in 1985-1989, 243 in 1990-1994, 299 in 1995-1999 and 407 in 2000-2001. Median length of stay in hospital also remained constant (Table 3.4).

Table 3.4 Hospitalisation for any reason in uninfected children

Year of birth	Children hospitalised (n)	Hospital admissions (n)	Follow-up (child-years)	Admissions per 1000 child-years follow-up (95% CI)	Median number of days in hospital (interquartile range)
1985-1989	89	118	447	264 (224-307)	8 (13)
1990-1994	65	91	374	243 (201-290)	7 (12)
1995-1999	92	129	431	299 (256-345)	8 (12)
2000-2001	62	88	216	407 (341-476)	10 (18)

3.6 Key points

- two thirds of children were born to white women, though the proportion of children born to black women (majority from sub-Saharan Africa) increased from 5% in 1985-1987 to 46% in 2000-2002
- half the children had mothers with intravenous drug use-related HIV infection, though HIV high-prevalence country acquired infection (majority from sub-Saharan Africa) increased over the study period
- 4% of children were born to women who had progressed to AIDS by the time of enrolment
- the majority of children (89%) had lived with one or both of their parents from birth up to their last assessment in the first year of life
- the most common type of alternative care was non-parental relatives
- the proportion of children who had been in alternative care decreased from 17% in 1985-1987 to 5% in 2000-2002
- children born to women who had used illicit drugs in pregnancy were more likely to have spent time in alternative care than children whose mothers had no reported drug use, after adjusting for maternal ethnicity, age and clinical status
- a total of 135 (8%) infants experienced at least one moderate/severe infective episode requiring medical attention in the first year of life; there was little correlation between recorded socio-demographic and child characteristics, and risk of the infant having a moderate/severe infective episode
- hospitalisation for any reason remained relatively stable over the study period

Chapter 4 Exposure to antiretroviral therapy and the health of uninfected children

"I strongly feel that it's very important to follow up on our children since nobody knows what the long term effects of these drugs can be."

[Mother of two children (aged 3 and 7 years)]

"If they think there are problems then it [follow-up] *is important. If there aren't side effects then it is wasting time."*

[Mother of four children (aged 2, 3, 11 and 14 years)]

4.1 Introduction

The risk of mother-to-child transmission (MTCT) of HIV infection is significantly reduced by the use of prophylactic antiretroviral therapy (ART) in the antenatal, intrapartum and neonatal periods (Connor *et al.* 1994, Mandelbrot *et al.* 2001, Cooper *et al.* 2002, European Collaborative Study 2005c). HIV infected pregnant women may also require highly active antiretroviral therapy (HAART) for their own health. Concerns have been raised that exposure to ART could have adverse effects on the fetus and newborn, both in the short- and long-term (Blanche *et al.* 1999, Olivero *et al.* 1997, Mofenson and Munderi 2002). In this chapter, ART exposure in uninfected children enrolled in the European Collaborative Study (ECS) is described; and health outcomes in these children, with respect to ART exposure, are assessed.

4.2 Methods

The analyses presented here were based on data on uninfected children enrolled in all ECS centres (obstetric and paediatric), apart from the analysis of longer-term health outcomes (Section 4.6) which was restricted to those enrolled in paediatric centres. The ECS methodology and general definitions used are given in Section 2.1. In addition, neonatal anaemia was defined as grade 2 or 3 toxicity according to the Pediatric AIDS Clinical Trials Group (PACTG) toxicity tables, which take into account age of the infant at the time of haemoglobin quantification (Division of AIDS (DAIDS) 2005). Low birth weight was defined as less than 2500g. Clinical symptoms in the child reported at each assessment were categorised into four groups: "not symptomatic", "mildly symptomatic", "moderately symptomatic" and "severely symptomatic", modelled on the Centers for Disease Control and Prevention (CDC) 1994 Revised Classification System for HIV Infection in Children Less Than 13 Years of Age (Centers for Disease Control and Prevention 1994) and designed to capture symptoms suggestive of mitochondrial

dysfunction (including febrile seizures) (Landreau-Mascaro *et al.* 2002, Dominguez *et al.* 2000), malignancies (Olivero *et al.* 1997) and other major infections (European Collaborative Study 2004b).

Univariable comparisons for categorical variables were tested with χ^2 tests or χ^2 tests for linear trend. Univariable and multivariable logistic regression was used to obtain odds ratios (OR), adjusted odds ratios (AOR) and 95% confidence intervals (CI). Analyses were performed using SAS statistical software (version 6.12, SAS Institute, Cary, North Carolina, USA).

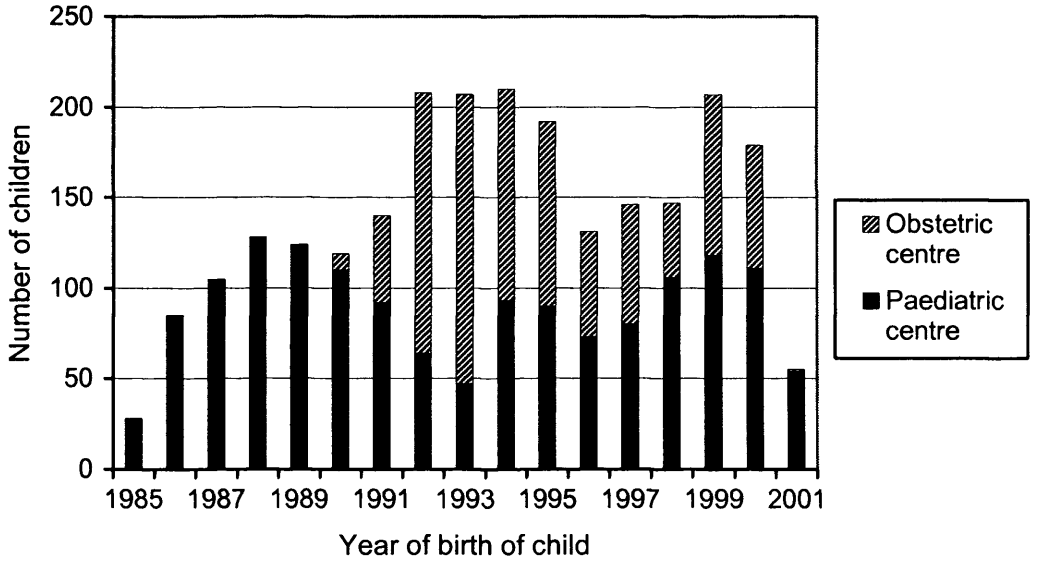
4.3 Pregnancy and delivery characteristics of mother-child pairs

By December 2001, 2414 uninfected children born to 2251 mothers had been enrolled in the ECS. Pregnancy and delivery characteristics are shown in Table 4.1. Of the 2414 children, 1511 (63%) had been enrolled in paediatric centres and 903 (37%) in obstetric centres (Figure 4.1).

Table 4.1 Pregnancy and delivery characteristics of mother-child pairs

	n (%)
Maternal age (years) (n=2174)	
<25	649 (30)
25-29	841 (39)
>29	684 (31)
Maternal illicit drug use (IDU) (n=2226)	
Never	1007 (45)
Past user/user timing unknown	782 (35)
Current	437 (20)
Mode of delivery (n=2386)	
Vaginal	1319 (55)
Emergency caesarean section	245 (10)
Elective caesarean section	822 (34)

Figure 4.1 Enrolment of uninfected children in the European Collaborative Study by year of birth and type of centre (by the end of 2001)



Maternal CD4 cell counts during pregnancy were available for 976 mother-child pairs (976/2414, 40%). The majority (83%) of the tests taken nearest to delivery were carried out in the third trimester. Maternal CD4 cell count was <200 cells/mm^3 in 14% (134/976) of mother-child pairs.

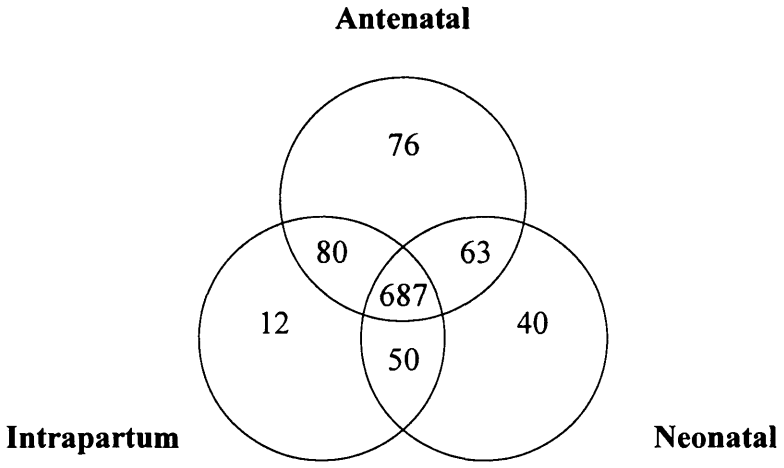
4.4 Antiretroviral therapy exposure

Of the 2414 children, 687 (28%) were exposed to ART during the antenatal, intrapartum and neonatal periods. A further 193 (8%) children were exposed to ART in two periods and 128 (5%) in one period. Of the 1008 exposed children, 906 (90%) were exposed antenatally, 840 (83%) neonatally and 829 (82%) in the intrapartum period (Figure 4.2). A total of 1406 (1406/2414, 58%) infants were not exposed to any ART, and of these, 113 were born after 1994 and therefore after publication of the results of the PACTG 076 trial (Connor *et al.* 1994). These 113 infants were not clustered in particular centres. A

total of 89 (79%) of them were born to white women, and median maternal age was 29.0 years (range 18.7-39.5).

The proportion of infants exposed to any ART significantly increased, from 23% (49/210) in 1994 to 78% (102/131) in 1996, 97% (143/147) in 1998 and 100% (179/179) in 2000 (χ^2_{trend}, 23.82, $p<0.001$).

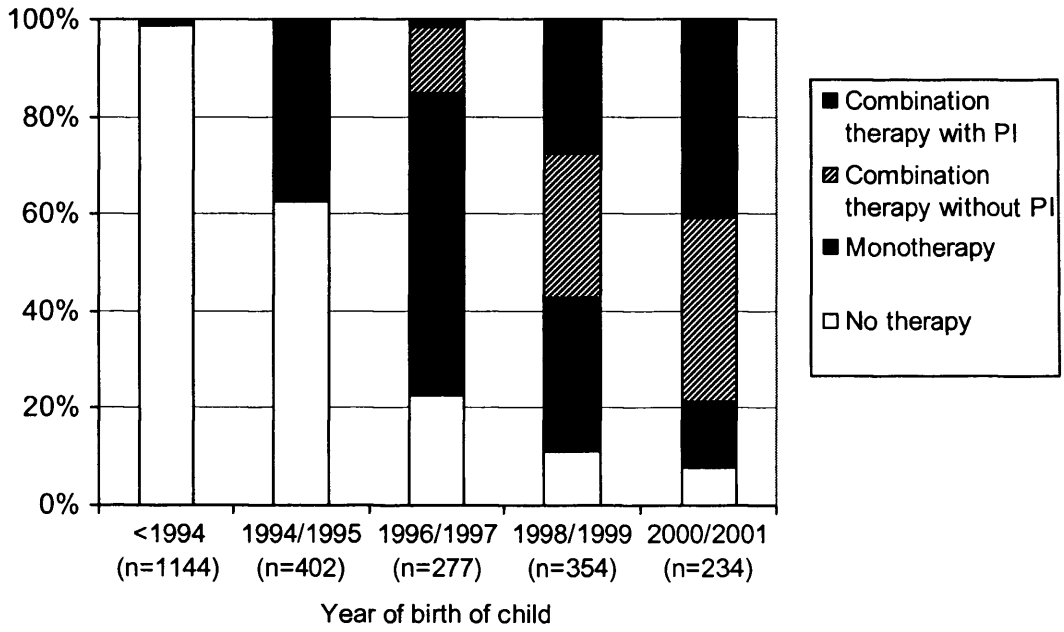
Figure 4.2 Antiretroviral therapy exposed children: periods of exposure (n=1008)



Zidovudine (ZDV) for six weeks according to the PACTG 076 regimen (Connor *et al.* 1994) was the most common neonatal ART; in one centre the neonatal regimen consisted of intravenous ZDV for 10 days (Grosch-Worner *et al.* 2000). Of the infants exposed to intrapartum ART, the majority were exposed to ZDV only (726/829, 88%), with 70 (8%) exposed to ZDV + nevirapine (NVP), 20 (2%) to ZDV + lamivudine (3TC) and the remaining 13 (2%) to 10 different drug combinations.

Of the 906 infants exposed to antenatal ART, 52% (475/906) were exposed to ZDV monotherapy and 48% (431/906) to combination therapy. Exposure to combination therapy increased over the study period (Figure 4.3). Of the 123 infants exposed to double therapy, the majority (n=92, 75%) were exposed to ZDV + 3TC; 13 were exposed to 3TC + stavudine (d4T), 11 to ZDV + didanosine (ddI), and the remaining seven to six different drug combinations.

Figure 4.3 Antenatal antiretroviral therapy exposure by year of birth of child



PI, protease inhibitor

Exposure to three or more antiretroviral drugs occurred in 308 infants. Drugs used in regimens with nucleoside analogue reverse transcriptase inhibitor (NRTI) backbones were: ZDV, 3TC, d4T, ddI, zalcitabine (ddC) and abacavir (ABC). NVP was the most commonly used non-nucleoside reverse transcriptase inhibitor (NNRTI) (n=63). Three infants were exposed to efavirenz (EFV); in all cases the drug had been started pre-conception, but was stopped early on in the pregnancy. A total of 194 infants were

exposed to a protease inhibitor (PI). The most frequently used PI was nelfinavir (NFV) (n=127, 65%), followed by indinavir (IDV), saquinavir (SQV) and ritonavir (RTV).

Information on the timing of initiation of antenatal ART was available for the mothers of 713 children (713/906, 79%). Of these, 139 (19%) infants were exposed to ART at conception: 31 to monotherapy and 108 to combination therapy. A total of 114 (16%) infants were born to women who initiated ART in the first trimester, 231 (32%) in the second and 229 (32%) in the third. Furthermore, exposure to ART at conception was more likely later in the study period (1998-2001) (108/471, 23%) than earlier (1994-1997) (30/241, 12%) (χ^2, 11.21, $p<0.001$). Of the 193 children where information on the timing of antenatal ART exposure was not available, 143 (74%) were exposed to monotherapy and 50 (26%) to combination therapy.

The proportion of children exposed to antenatal ART did not significantly differ between paediatric (559/1511, 37%) and obstetric (347/903, 38%) centres (χ^2, 0.49, $p=0.482$).

4.5 Early health outcomes

4.5.1 Congenital abnormalities

Congenital abnormalities were recorded in 37 (1.5%) out of the 2414 children, 13 of whom had been exposed to ART antenatally (Table 4.2). Of the exposed children, seven had been exposed in the first trimester: a child with Down's syndrome (ZDV + 3TC), two with a ventricular septal defect (AZT + 3TC, ZDV + 3TC + D4T + NVP), and one with hydronephrosis (ZDV + 3TC + NVP). The remaining three children exposed in the first trimester had unspecified anomalies at birth, but in follow-up assessments one was reported to have ileostoma and enteritis (ZDV + 3TC + NVP) and one an atrial septal defect (ZDV + 3TC + RTV); no further clinical information was available for the third

child (ZDV + 3TC). The pattern and prevalence of abnormalities in infants exposed to antenatal ART (13/906, 1.4%) was similar to those not exposed (24/1508, 1.6%) (χ^2, 0.09, p=0.762) (Table 4.2). The prevalence of congenital abnormalities in children exposed to ART in the first trimester (7/253, 2.8%) was similar to that in those exposed in the second or third trimester (6/460, 1.3%) (Fisher exact test, p=0.163).

Table 4.2 Children with a congenital abnormality by antenatal antiretroviral therapy exposure (n=37)

Congenital abnormality	Not exposed to antenatal ART (n)	Exposed to antenatal ART in the first trimester (n)	Exposed to antenatal ART in the second or third trimester (n)
Polycystic kidney	2		1
Ventricular septal defect	4	2	1
Multiple intracardiac tumours	1		
Situs inversus	1		
Cleft palate	1		
Hydrocephalus	1		
Down's syndrome		1	2
Cateract	1		
Hydronephrosis	1	1	
Microcephaly	1		
Fallot tetrology	1		
Oesophageal atresia	2		
Polydactyly	3		1
Unspecified abnormalities	5	3	1
Total	**24**	**7**	**6**

ART, antiretroviral therapy

4.5.2 Low birth weight

Birth weight was available for 97% of enrolled children (2339/2414): mean 2927g (SD 561) and median 2950g (range 735-5300). Nineteen percent (449/2339) of infants had low birth weight (LBW) (<2500g) and of these, 33 had very low birth weight (VLBW) (<1500g). There was no association between antenatal ART exposure and LBW: 18%

(160/874) of those exposed were of LBW compared with 20% (289/1465) of those not exposed (χ^2, 0.71, p=0.399). Of the 33 infants with VLBW, 14 had been exposed to antenatal ART and 19 were not exposed.

4.5.3 Requirement for a blood transfusion

Thirty-two infants required a blood transfusion in the immediate postpartum period: 1.2% (11/906) of the antenatally exposed infants and 1.4% (21/1508) of those not exposed. There was no association between antenatal ART exposure and the need for a blood transfusion (χ^2, 0.14, p=0.710). One infant required a transfusion following surgery, five had anaemia, one had thrombocytopenic purpura, 20 were premature, and for five the reason was not recorded.

4.5.4 Prematurity

Gestational age information was available for 2326 children (2326/2414, 96%). Of the 88 children with no information, 22 (25%) had been exposed to antenatal ART and 66 (75%) had not been exposed.

The overall crude prematurity (gestational age <37 weeks) rate was 17% (396/2326), and this increased from 16% (73/460) in 1985-1989 to 25% (178/710) in 1997-2001. For infants not exposed to antenatal ART, the crude prematurity rate was 15% (221/1442); for infants exposed to monotherapy it was 16% (75/465) and for those exposed to combination therapy it was 24% (100/419) (χ^2, 17.09, p<0.001).

Antenatal ART exposure was significantly associated with prematurity in multivariable logistic regression analysis (Table 4.3).

Table 4.3 Risk factors for prematurity (gestational age <37 weeks) in children enrolled in obstetric and paediatric centres

	Prematurity					
	No (%)	Yes (%)	Unadjusted odds ratio		Adjusted odds ratio*	
			(95% CI)	p value	(95% CI)	p value
Antenatal ART exposure						
None	1221 (85)	221 (15)	1.00		1.00	
Monotherapy	390 (84)	75 (16)	0.73 (0.43-1.24)	p=0.242	0.90 (0.51-1.58)	p=0.704
Combination therapy without PI	182 (79)	49 (21)	2.00 (1.20-3.31)	p=0.008	2.66 (1.52-4.67)	p=0.001
Combination therapy with PI	137 (73)	51 (27)	3.45 (2.08-5.72)	p<0.001	4.14 (2.36-7.23)	p<0.001
	χ^2=19.66, p<0.001					
Maternal illicit drug use						
Never	841 (86)	138 (14)	1.00		1.00	
Past user/user timing unknown	622 (82)	137 (18)	1.12 (0.74-1.71)	p=0.596	1.37 (0.87-2.14)	p=0.175
Current user	324 (77)	96 (23)	1.72 (1.05-2.81)	p=0.031	2.76 (1.56-4.86)	p<0.001
	χ^2=16.45, p<0.001					
Maternal CD4 cell count (cells/mm^3)						
≥ 500	316 (87)	49 (13)	1.00		1.00	
200-499	396 (83)	81 (17)	1.14 (0.76-1.71)	p=0.536	1.04 (0.68-1.59)	p=0.849
<200	109 (81)	25 (19)	1.32 (0.76-2.29)	p=0.324	1.22 (0.69-2.17)	p=0.500
	χ^2=2.85, p=0.240					
Maternal age (years)						
<25	527 (84)	99 (16)	1.00		1.00	
25-29	694 (85)	126 (15)	0.79 (0.48-1.30)	p=0.355	0.75 (0.44-1.26)	p=0.276
>29	531 (80)	133 (20)	1.26 (0.78-2.03)	p=0.342	1.10 (0.66-1.84)	p=0.724
	χ^2=6.50, p=0.039					

The univariable and multivariable odds ratio included 864 mother-child pairs with complete information on antenatal ART exposure, maternal illicit drug use, CD4 cell count and age. *Adjusted for all other variables in model. CI, confidence interval; ART, antiretroviral therapy; PI, protease inhibitor.

Adjusting for maternal CD4 cell count, illicit drug use (IDU) and age, children exposed to combination therapy without a PI were more likely to be born prematurely than children not exposed to antenatal ART (AOR 2.66, 95% CI 1.52-4.67); and the association was more pronounced in children exposed to combination therapy with a PI (AOR 4.14, 95% CI 2.36-7.23).

Elective caesarean section is recommended for HIV infected pregnant women to reduce the risk of MTCT, and here median gestational age for infants delivered by elective caesarean section was 38 weeks. The logistic regression analysis was repeated with mode of delivery included (categorised into elective caesarean section, emergency caesarean section, vaginal delivery): the AORs reduced a little to 2.05 (95% CI 1.10-3.84) following exposure to combination therapy without a PI, and to 3.15 (95% CI 1.68-5.92) following exposure to combination with a PI.

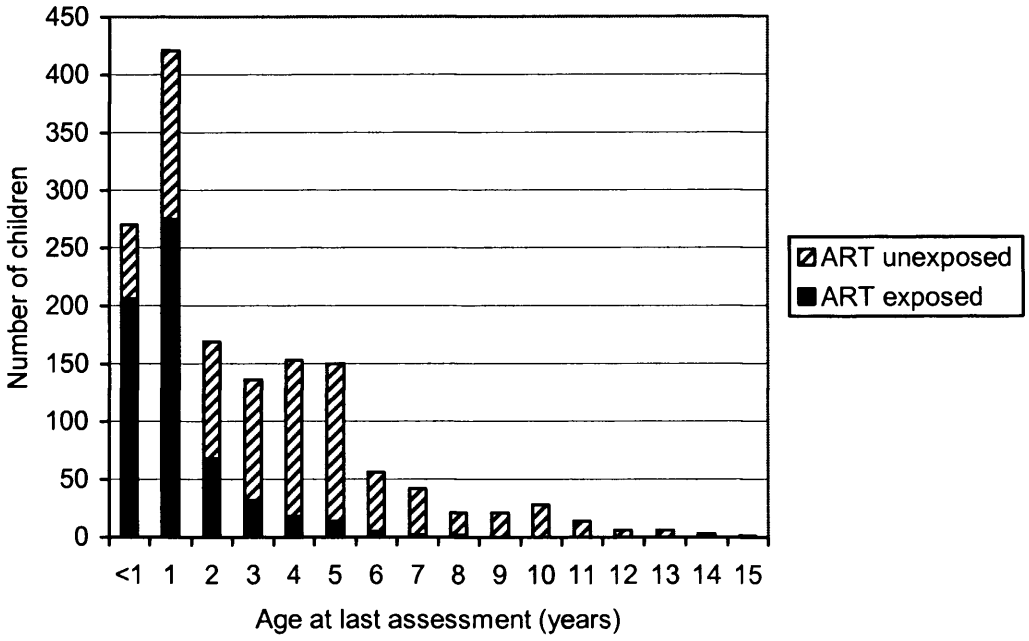
4.6 Longer-term health outcomes reported in follow-up assessments

The 1511 uninfected children enrolled in paediatric centres (see Section 4.3) had a median length of clinical follow-up of 2.2 years (range 0-15.9) and a combined length of follow-up of 4840 child-years (Figure 4.4).

4.6.1 Anaemia

Information on haemoglobin levels in the first six weeks of life was available for 763 of the 1511 infants (50%). Allowing for age at assessment, ART exposure during the antenatal, intrapartum or neonatal period was strongly associated with a diagnosis of anaemia (see Section 4.2): 33% (153/458) in exposed infants compared with 12% (38/305) in unexposed infants (χ^2, 42.81 $p<0.001$).

Figure 4.4 Age at which children enrolled in paediatric centres were last seen for a follow-up assessment (by the end of 2001)



ART, antiretroviral therapy

4.6.2 Clinical symptoms

Clinical follow-up information, from which symptoms were categorised in terms of possible ART-associated toxicity (Section 4.2), was available for 1497 (99%) of the 1511 children enrolled in paediatric centres. Total length of follow-up in the first 18 months of life for the 1497 children was 1909 child-years. Of the 14 children with no clinical follow-up information, three were born to mothers who had taken ART during pregnancy and the remainder were not exposed to any ART.

Follow-up assessments in the first 18 months of life

Severe clinical symptoms

Six children (6/1497, 0.4%), none of whom had been exposed to any ART, had severe clinical symptoms in the first 18 months of life. Of these, one child had epilepsy (Child 1

in Table 4.4) and two had febrile seizures (Children 2 and 3). A fourth child had infantile spasms (West syndrome) at 34 weeks of age, which then persisted with severe mental retardation (Child 4); and a fifth child had perinatal encephalopathy attributed to asphyxia and fetal alcohol syndrome (Child 5). One infant had encephalopathy (paresis, pathologic reflexes, increased tone, leucomalacia) at five weeks of age and died of sudden infant death syndrome (SIDS) at 22 weeks of age (Child 6).

Moderate clinical symptoms

A total of 240 children (240/1497, 16%) had moderate clinical symptoms (in terms of possible ART-associated toxicity) in the first 18 months of life. Most of these conditions consisted of one episode of an infection requiring medical attention such as: diarrhoea, candidiasis, bacterial meningitis, pneumonia or sepsis, unexplained fever. Of these 240 children, 80 with 115 child-years of follow-up were exposed to ART (antenatal, intrapartum or neonatal) (incidence rate 0.696 cases per child-year) and 160 with 223 child-years of follow-up were not exposed (incidence rate 0.717 cases per child-year) (rate ratio 0.970, p=0.827).

Factors associated with moderate/severe clinical symptoms or death in the first 18 months of life

In multivariable logistic regression analysis, children with severe/moderate symptoms and/or who had died (three children died, see Section 4.6.3) were compared with children with mild/no symptoms. A child's most severe clinical category reached during follow-up in the first 18 months of life was considered in analysis. In order to maximise the follow-up data available for analysis, children were included regardless of whether they had reached 18 months of age at the time of analysis. There were 117 (7.7%, 117/1511) children born less than 18 months before the time of analysis. Children

exposed to ART during the antenatal, intrapartum or neonatal period were no more likely to experience moderate/severe symptoms or die in the first 18 months of life than children who were not exposed to any ART (AOR 1.42, 95% CI 0.71-2.84, p=0.320), after adjusting for year of birth of the child and maternal IDU, ethnicity and age (Table 4.5). Children born 1999-2001 were less likely to have moderate/severe symptoms or die than those born early in the study period (AOR 0.37, 95% CI 0.16-0.87, p=0.022). This finding could reflect the fact that not all children within this category reached 18 months of age and therefore may yet have developed clinical symptoms.

Follow-up assessments after the first 18 months of life

In addition to the six children who had severe clinical symptoms in the first 18 months of life, five other children had severe clinical symptoms at later ages. One unexposed child had febrile seizures at 3.3 years (Child 7 in Table 4.4) and one had tuberculosis at 1.7 years of age (Child 8). Two unexposed children had malignancies during follow-up: one had Hodgkin's lymphoma at three years and another had a brain tumour (giant cell astrocytoma) at 11 years of age; no later assessments were conducted for either child (Children 9 and 10 respectively). The fifth child had static encephalopathy at 6.8 years of age; though no later assessments were conducted. The child's mother had taken ZDV from 16 weeks gestation, but the child had not been exposed to ART in the intrapartum or neonatal periods (Child 11).

Forty-two children had moderate clinical symptoms after 18 months of age, of whom 13 had been exposed to ART in the antenatal, intrapartum or neonatal period.

Table 4.4 Details of children who had severe clinical symptoms or who died

Child	Clinical symptoms and age at assessment	Vital status at last assessment	Antiretroviral therapy exposure	Maternal illicit drug use in relation to the pregnancy	Age at last assessment
1	Epilepsy at 27 weeks	Alive	None	IDU in pregnancy	5.6 years
2	Febrile seizures at 1.3 years	Alive	None	Ex-IDU	6.1 years
3	Febrile seizures at 40 weeks	Alive	None	None	2.6 years
4	Infantile spasms (West syndrome) at 34 weeks	Alive	None	IDU in pregnancy	5.1 years
5	Perinatal encephalopathy (attributed to asphyxia and fetal alcohol syndrome) at 15 weeks	Alive	None	Ex-IDU	2.8 years
6	Encephalopathy (paresis, pathologic reflexes, increased tone, leucomalacia) at 5 weeks	Died of sudden infant death syndrome (SIDS) at 22 weeks	None	None	22 weeks
7	Febrile seizures at 3.3 years	Alive	None	Ex-IDU	15.9 years
8	Tuberculosis at 1.7 years	Alive	None	None	5.0 years
9	Hodgkin's lymphoma at 3.1 years	Alive	None	IDU in pregnancy	3.1 years
10	Malignancy of the brain at 11.1 years	Alive	None	IDU in pregnancy	11.1 years
11	Static encephalopathy at 6.8 years	Alive	ZDV during pregnancy	None	6.8 years

IDU, illicit drug user
ZDV, zidovudine

Table 4.4 continued

Child	Clinical symptoms	Vital status at last assessment	Antiretroviral therapy exposure	Maternal illicit drug use in relation to the pregnancy	Age at last assessment
12	No symptoms. Gestational age 39 weeks and birth weight 3310g	Died at 25 weeks. Cause of death not reported	None	IDU in pregnancy	25 weeks
13	No symptoms. Gestational age 37 weeks and birth weight 2900g	Died of group A beta haemolytic streptococcal septicaemia at 2.6 years	None	Ex-IDU	2.6 years
14	No symptoms. Gestational age 34 weeks and birth weight 2510g	Died at 17 weeks. Cause of death not reported	ZDV + 3TC in pregnancy; and ZDV for neonate	Ex-IDU	17 weeks

IDU, illicit drug user
ZDV, zidovudine
3TC, lamivudine

Table 4.5 Factors associated with moderate/severe clinical symptoms or death in the first 18 months of life

	Clinical symptoms					
	Mild/no symptoms (%)	Moderate/severe symptoms or death (%)	**Unadjusted odds ratio (OR)** (95% CI)	p value	**Adjusted odds ratio (AOR)*** (95% CI)	p value
ART exposure						
No	701 (81)	166 (19)	1.00		1.00	
Yes	549 (87)	81 (13)	0.65 (0.48-0.87)	p=0.005	1.42 (0.71-2.84)	p=0.320
	χ^2=10.48, p=0.001					
Maternal illicit drug use						
Never	620 (86)	104 (14)	1.00		1.00	
Past user/user timing unknown	348 (80)	85 (20)	1.58 (1.14-2.19)	p=0.006	1.21 (0.81-1.82)	p=0.355
Current user	222 (81)	52 (19)	1.44 (0.99-2.11)	p=0.058	0.97 (0.61-1.54)	p=0.891
	χ^2=6.47, p=0.039					
Maternal ethnicity						
White	820 (82)	180 (18)	1.00		1.00	
Black	314 (87)	48 (13)	0.62 (0.43-0.88)	p=0.008	0.85 (0.55-1.33)	p=0.477
Other	68 (88)	9 (12)	0.66 (0.32-1.36)	p=0.264	0.83 (0.39-1.76)	p=0.626
	χ^2=5.69, p=0.058					
Maternal age (years)						
<25	347 (78)	98 (22)	1.00		1.00	
25-29	424 (86)	71 (14)	0.55 (0.39-0.78)	p<0.001	0.60 (0.42-0.85)	p=0.004
>29	360 (86)	59 (14)	0.57 (0.40-0.82)	p=0.002	0.72 (0.49-1.07)	p=0.101
	χ^2=13.05, p=0.001					
Year of birth						
1985-1989	356 (76)	112 (24)	1.00		1.00	
1990-1993	259 (84)	48 (16)	0.62 (0.42-0.92)	p=0.017	0.70 (0.46-1.06)	p=0.094
1994-1998	384 (88)	54 (12)	0.55 (0.38-0.79)	p=0.001	0.51 (0.25-1.03)	p=0.059
1999-2001	249 (89)	32 (11)	0.44 (0.28-0.69)	p<0.001	0.37 (0.16-0.87)	p=0.022
	χ^2=29.84, p<0.001					

The univariable and multivariable odds ratio included 1320 mother-child pairs with complete information on ART exposure, year of birth; and maternal illicit drug use, ethnicity and age. *Adjusted for all other variables in model. CI, confidence interval; ART, antiretroviral therapy.

4.6.3 Deaths

Four children died during follow-up. One child not exposed to any ART died at 25 weeks of age though the cause of death was not reported (Child 12 in Table 4.4), and another unexposed child died of group A beta haemolytic streptococcal septicaemia at 2.6 years of age (Child 13). The only exposed child that died during follow-up had been exposed to ZDV + 3TC antenatally and ZDV neonatally, however the cause of death was not reported (Child 14). The fourth child died of SIDS at 22 weeks and was described in Section 4.6.2 (Child 6).

4.7 Key points

- just under a third of infants were exposed to ART during the antenatal, intrapartum and neonatal periods; 8% were exposed in two periods and 5% in only one
- the proportion of children exposed to any ART increased from 23% in 1994 to 100% in 2000
- of the 906 infants exposed to antenatal ART, half were exposed to ZDV monotherapy and half to combination therapy; and exposure to combination therapy increased over the study period
- exposure to ART at conception was more likely later in the study period than earlier
- 37 (1.5%) infants had congenital abnormalities; the pattern and prevalence of abnormalities in infants exposed to antenatal ART was similar to those not exposed
- there was no association between antenatal ART exposure and low birth weight, or requirement for a blood transfusion in the immediate postpartum period
- adjusting for maternal CD4 cell count, IDU and age, children exposed to combination therapy with or without a PI were more likely to be born prematurely than children not exposed to antenatal ART

- allowing for age at assessment, ART exposure during the antenatal, intrapartum or neonatal period was associated with anaemia in the first six weeks of life
- in the first 18 months of life, six children, none of whom had been exposed to any ART, had severe clinical symptoms; and 240 children had moderate clinical symptoms, of whom 80 with 115 child-years of follow-up were exposed to ART and 160 with 223 child-years of follow-up were not exposed (rate ratio 0.970, p=0.827)
- children exposed to ART during the antenatal, intrapartum or neonatal period were no more likely to experience moderate/severe symptoms or die in the first 18 months of life than children who were not exposed to any ART, after adjusting for year of birth of the child and maternal IDU, ethnicity and age
- two children had malignancies diagnosed after 18 months of age, neither were exposed to any ART
- four children died during follow-up, one of whom had been exposed to ZDV + 3TC antenatally and ZDV neonatally

Chapter 5 Exposure to antiretroviral therapy and growth in uninfected children

"I sometimes think she's too skinny and wonder if it's the drugs. My other babies are chubby."

[Mother of three children (aged 1, 3 and 12 years)]

5.1 Introduction

There is only limited information on whether antiretroviral therapy (ART) exposure has an adverse effect on growth in uninfected children born to HIV infected women in resource-rich settings. Initial reports addressing growth after zidovudine exposure were reassuring (Sperling *et al.* 1998, Culnane *et al.* 1999, Chotpitayasunondh *et al.* 2001), but uninfected children are increasingly exposed antenatally to highly active antiretroviral therapy (HAART), often throughout the whole gestational period (European Collaborative Study 2004a). Although antenatal ART exposure has not been observed to be associated with fetal growth (Fiore 2005), combination therapy, particularly HAART, has consistently been associated with prematurity in European cohorts (see Chapter 4) (Lorenzi *et al.* 1998, European Collaborative Study 2004a). In this chapter, weight, length/height and head circumference (occipitofrontal circumference, OFC) measurements in the first 18 months of life in uninfected children enrolled in the European Collaborative Study (ECS) paediatric centres are assessed, while allowing for maternal characteristics and antenatal ART exposure.

5.2 Methods

The general ECS methodology and definitions are outlined in Section 2.1. Weight and OFC were recorded at birth, and weight, length/height and OFC were recorded at each subsequent follow-up assessment (European Collaborative Study 1995). A z-score (standard deviation from the mean of a population) for each measurement of weight, length/height and OFC was calculated according to age and gender using the LMS method. The LMS method summarises the changing distribution of a variable over age, by curves that represent the median, coefficient of variation and skewness (Cole and Green 1992). The use of z-scores means that measurements are no longer age-dependent and therefore maximises the data available for analysis. As all children in this analysis

were born to HIV infected women, z-scores were calculated from within this population. In the calculation of z-scores, no adjustment was made for gestational age as this was a variable of particular interest given its association with HAART (European Collaborative Study 2004a).

Twins and triplets (n=75) were excluded for this analysis because of their different growth patterns and propensity for premature delivery compared with singletons. For the 75 twins and triplets, mean birth weight was 2065g (SD 456g) and 77% (58/75) of them had a gestational age of less than 37 weeks.

An unpaired t-test was used to compare mean z-scores at birth. The Kaplan-Meier method (Kaplan and Meier 1958) was used to calculate survival estimates for the age at the first assessment where the child's z-score exceeded the 25th centile within this population (i.e. z-score of $\geq$-0.6745), for weight and OFC. The log rank test was used to test statistical significance between strata. Children were censored at the age they were last measured within the first 18 months of life. Linear mixed effects regression models which allowed for repeated measures were used to investigate the effect of neonatal and maternal characteristics including antenatal ART exposure, on weight, length/height and OFC. The likelihood ratio test was used to assess the fit of models. The Akaike's information criterion (AIC) was used to assess the improvement of models with inclusion of additional random effects on centre level.

Z-scores were calculated using LMS program (version 1.16, Institute of Child Health, London, UK). Analyses were conducted using SAS statistical software (version 8.02, SAS Institute, Cary, North Carolina, USA), STATA (version 8.2, Statacorp, College

Station, Texas, USA) and R statistical software (version 1.91, R Foundation for Statistical Computing, Vienna, Austria).

5.3 Results

By December 2003, 1912 uninfected singleton children (51%, n=972 male) born to 1728 mothers had been enrolled in ECS paediatric centres (Table 5.1). Of the 78 children with a gestational age of less than 34 weeks, 51 were born at 33 or 32 weeks, 20 at 31 or 30 weeks, three at 29 weeks, two at 28 weeks and two at 27 weeks. ART was initiated before pregnancy in 8% (26/317) of the 317 infants with monotherapy exposure, in 18% (23/125) of the 125 with double therapy exposure, and in 41% (200/483) of the 483 with HAART exposure.

5.3.1 Weight, length/height and head circumference

From birth to 18 months of age there were 11050 weight measurements for 1899 children (mean, 5.8 per child), 8523 length/height measurements for 1776 children (mean, 4.8 per child) and 8928 OFC measurements for 1852 children (mean, 4.8 per child).

Cumulative length of follow-up to 18 months of age for 1513 term children (gestational age $\geq$37 weeks) was 1231 child-years for those with none/monotherapy antenatal ART exposure, and 418 child-years for those exposed to combination therapy; for the 344 premature children (gestational age <37 weeks) it was 216 child-years for those with none/monotherapy antenatal ART exposure, and 150 child-years for those exposed to combination therapy. Overall median length of follow-up was 1.2 years.

Table 5.1 Neonatal and maternal characteristics of mother-child pairs (n=1912)

	n (%)
Gestational age (weeks) (n=1857)	
<34	78 (4)
34-36	266 (14)
≥37	1513 (81)
Birth weight (g) (n=1856)	
<1500	22 (1)
1500-2499	299 (16)
≥2500	1535 (83)
Exposure to antenatal antiretroviral therapy (n=1912)	
None	987 (52)
Monotherapy	317 (17)
Double therapy	125 (7)
HAART	483 (25)
Maternal CD4 count nearest delivery (cells/mm^3) (n=744)	
≥500	212 (28)
200-499	407 (55)
<200	125 (17)
Maternal ethnicity (n=1849)	
White	1180 (64)
Black	561 (30)
Other	108 (6)
Maternal illicit drug use (IDU) (n=1812)	
Never	1048 (58)
Past user/user timing unknown	469 (26)
Current	295 (16)

To describe the patterns of the three growth measurements, z-scores for weight, length/height and OFC over age were plotted; and mean values of the z-scores by gestational age were calculated (Figures 5.1-5.3).

Figure 5.1 **Z-scores for weight with running-mean smoothing by gestational age category**

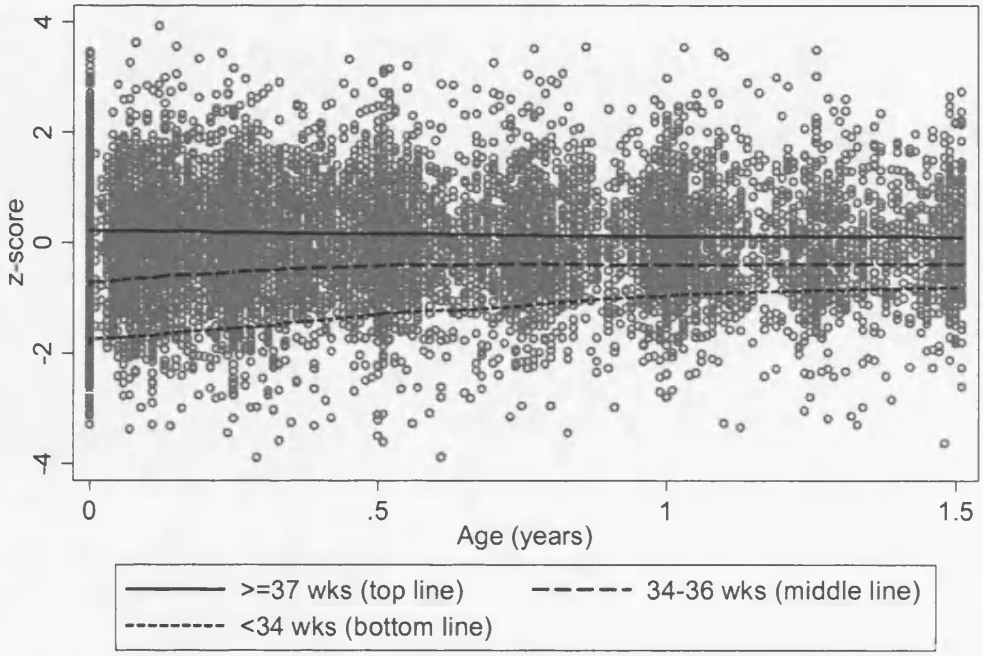


Figure 5.2 **Z-scores for length/height with running-mean smoothing by gestational age category**

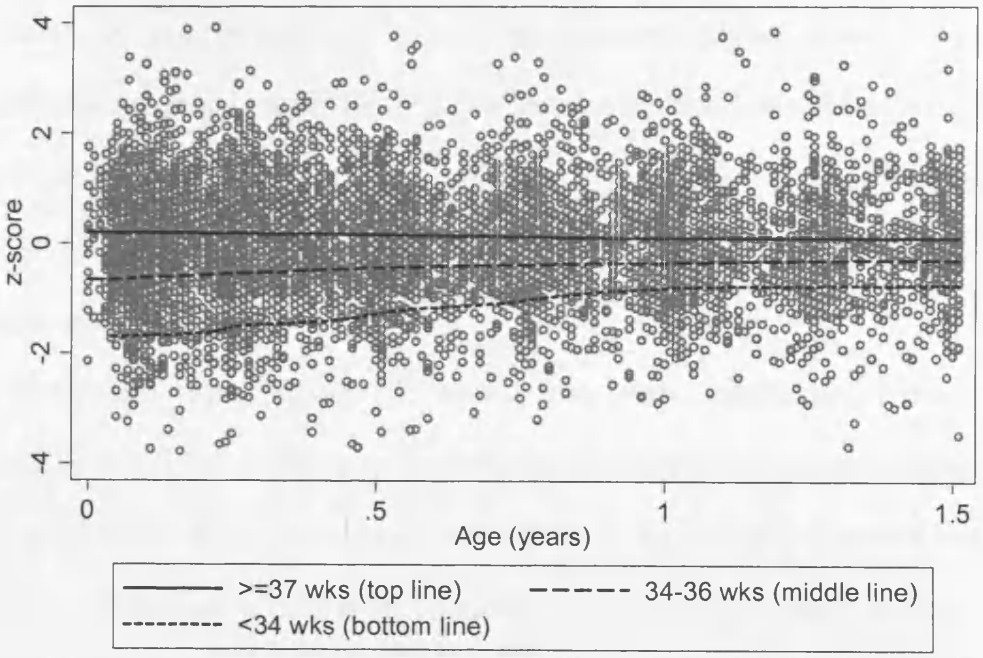
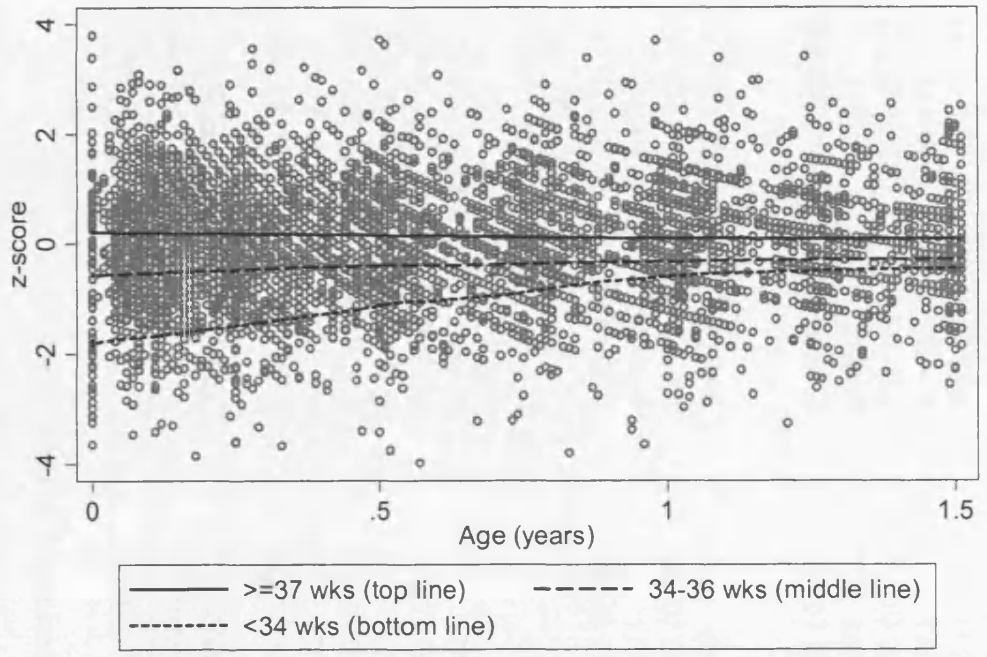


Figure 5.3 Z-scores for head circumference with running-mean smoothing by gestational age category



The analysis was further separated on two groups of antenatal ART exposure (none/monotherapy and combination therapy). Mean and standard deviation of z-scores at different age periods, stratified by gestational age and antenatal ART exposure are shown in Table 5.2.

Weight and OFC at birth

For term infants (gestational age ≥37 weeks), there was no significant difference in birth weight between infants with no or monotherapy exposure (mean z-score 0.26) and those with combination therapy exposure (mean z-score 0.23) (p=0.524); and there was no significant difference in OFC at birth between exposure groups: mean z-scores 0.15 and 0.25 respectively (p=0.121) (Table 5.2).

Table 5.2 Mean and standard deviation of z-score for weight, length/height and head circumference (OFC), at different age periods stratified by gestational age category and antenatal antiretroviral therapy exposure

	<34 weeks (mean (SD) *n*)		34-36 weeks (mean (SD) *n*)		≥37 weeks (mean (SD) *n*)	
	None or monotherapy	Combination therapy	None or monotherapy	Combination therapy	None or monotherapy	Combination therapy
Weight						
Birth	-1.91 (0.76) *n=49*	-2.06 (0.64) *n=26*	-0.95 (0.68) *n=142*	-0.71 (0.72) *n=121*	0.26 (0.92) *n=1039*	0.23 (0.80) *n=439*
<3 months	-1.62 (0.79) *n=51*	-1.81 (0.68) *n=26*	-0.77 (0.72) *n=144*	-0.55 (0.76) *n=121*	0.22 (0.83) *n=1053*	0.22 (0.70) *n=448*
15-18 months	-0.78 (1.24) *n=34*	-0.40 (1.08) *n=14*	-0.46 (0.99) *n=64*	-0.33 (1.05) *n=42*	0.03 (0.97) *n=567*	0.31 (1.05) *n=120*
Length*/ Height						
<3 months	-1.46 (1.03) *n=37*	-1.84 (0.73) *n=24*	-0.63 (0.83) *n=105*	-0.61 (0.78) *n=115*	0.24 (0.91) *n=760*	0.15 (0.78) *n=408*
15-18 months	-0.65 (1.22) *n=33*	-0.75 (1.26) *n=13*	-0.41 (0.93) *n=61*	-0.15 (0.99) *n=40*	0.03 (1.00) *n=525*	0.29 (1.14) *n=112*
OFC						
Birth	-1.95 (0.93) *n=37*	-1.93 (0.60) *n=18*	-0.76 (0.93) *n=117*	-0.51 (0.78) *n=106*	0.15 (0.91) *n=844*	0.25 (0.92) *n=321*
<3 months	-1.58 (0.92) *n=46*	-1.95 (0.63) *n=24*	-0.67 (0.86) *n=134*	-0.46 (0.71) *n=115*	0.21 (0.84) *n=982*	0.18 (0.81) *n=432*
15-18 months	-0.31 (1.22) *n=28*	-0.68 (0.77) *n=10*	-0.30 (0.84) *n=53*	0.05 (1.00) *n=30*	0.03 (0.97) *n=457*	0.04 (1.17) *n=87*

*Length was not recorded at birth; SD, standard deviation

Infants born at 34-36 weeks and exposed to combination therapy were significantly heavier at birth (mean z-score -0.71) than those with no or monotherapy exposure (mean z-score -0.95) ($p<0.001$). Infants born at 34-36 weeks and exposed to combination therapy had a larger OFC at birth (mean z-score -0.51) than those with no or monotherapy exposure (mean z-score -0.76) ($p=0.036$) (Table 5.2).

For children born before 34 weeks, there was no significant difference in birth weight between infants with no or monotherapy exposure (mean z-score -1.91) and those with combination therapy exposure (mean z-score -2.06) ($p=0.403$); and there was no significant difference in OFC at birth between exposure groups: mean z-scores -1.95 and -1.93 respectively ($p=0.939$) (Table 5.2).

Cumulative probability of reaching a given centile for weight and OFC

Cumulative probability of reaching the 25th centile for weight, stratified by gestational age category and antenatal ART exposure, is shown in Figure 5.4. An estimated 85% of all term children irrespective of ART exposure had already reached the 25th centile at birth (log rank test: $p<0.001$). An estimated 50% of those born at 34-36 weeks with combination therapy exposure had already reached the 25th centile at birth; and for children born at 34-36 weeks with no or monotherapy exposure, the estimated median age at reaching the 25th centile was just over three months of age (log rank test: $p=0.003$). For all children born before 34 weeks, the estimated median age at reaching the 25th centile was over a year regardless of exposure (log rank test: $p=0.944$).

A similar pattern occurred for OFC (Figure 5.5) for term children and those born at 34-36 weeks (log rank tests: $p=0.008$ and $p=0.004$ respectively); but for children born before 34 weeks, the estimated median age at reaching the 25th centile was fifteen months for

children with combination therapy exposure and just over seven months for those with no or monotherapy exposure (log rank test: p=0.004).

Figure 5.4 Probability of reaching the 25th centile for weight stratified by gestational age category and antenatal ART exposure

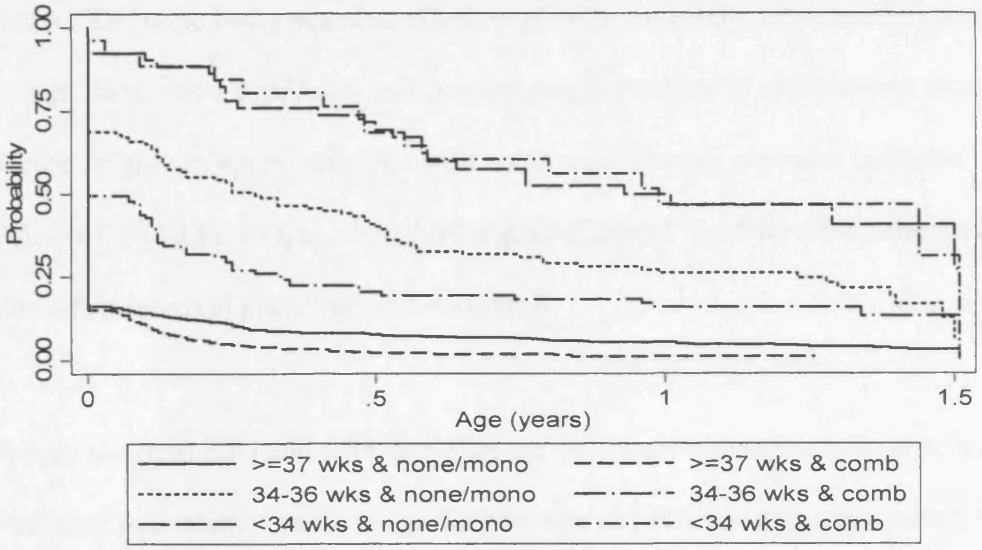
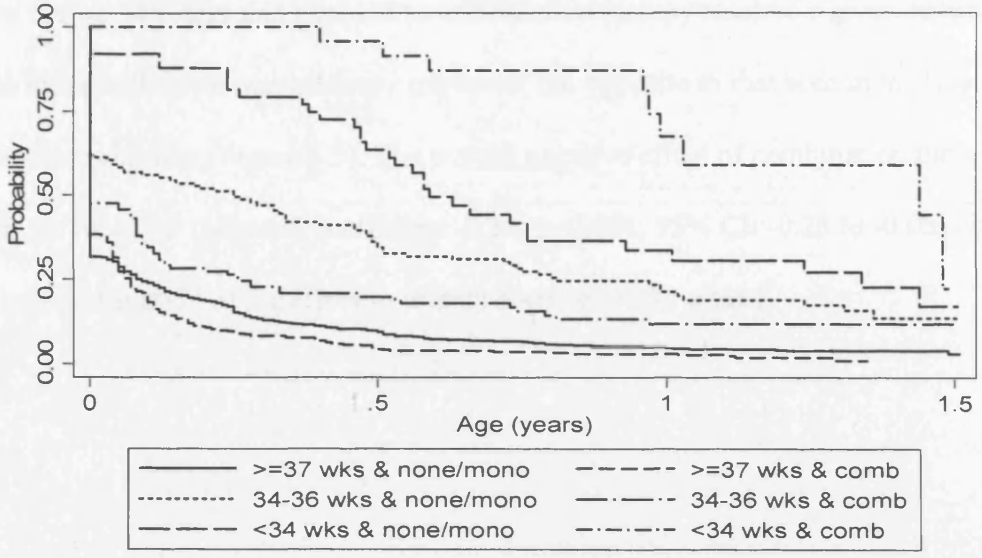


Figure 5.5 Probability of reaching the 25th centile for head circumference stratified by gestational age category and antenatal ART exposure



5.3.2 Factors associated with weight, length/height and head circumference in the first 18 months of life

To investigate factors associated with growth up to 18 months of age, regression models were fitted for weight, length/height and OFC (Tables 5.3-5.5). Prematurity (gestational age <37 weeks) had a negative effect on weight, length/height, and OFC. Maternal illicit drug use (IDU) also had a negative effect on growth, especially when used in pregnancy. Although there was a significant independent negative effect of combination therapy exposure on growth when compared with no or monotherapy exposure (adjusted coefficients: -0.10 for weight, -0.12 for length/height and -0.14 for OFC), the magnitude of this effect in actual measurements was small.

Although maternal IDU and ART exposure are both known determinants of prematurity, inclusion of two interaction terms (gestational age and IDU, gestational age and ART) in the models did not improve the fit of each model. The interaction between gestational age <34 weeks and ART in the OFC model was negative (coefficient -0.39, p=0.043, 95% CI: -0.77 to -0.01), in contrast to that of gestational age 34-36 weeks and ART (coefficient 0.26, p=0.012, 95% CI: 0.06 to 0.47). This reflects the finding that children born before 34 weeks and exposed to combination therapy reached a given centile later than those with no or monotherapy exposure; the opposite to that seen in the less premature children (Figure 5.5). The overall negative effect of combination therapy on OFC in Table 5.5 (adjusted coefficient -0.14, p=0.001, 95% CI: -0.23 to -0.06) could be an underestimation of the effect in infants born before 34 weeks.

Table 5.3 Weight (z-score) and maternal and infant factors in the first 18 months of life

	Unadjusted coefficient (95% CI)	*p value*	Adjusted coefficient* (95% CI)	*p value*
Antenatal ART exposure				
None/monotherapy	0.00		0.00	
Combination therapy	0.07 (-0.02, 0.15)	*p=0.133*	-0.10 (-0.18, -0.02)	*p=0.019*
Gestational age (weeks)				
≥ 37	0.00		0.00	
34-36	-0.70 (-0.80, -0.59)	*p<0.001*	-0.65 (-0.75, -0.55)	*p<0.001*
<34	-1.56 (-1.75, -1.38)	*p<0.001*	-1.51 (-1.68, -1.34)	*p<0.001*
Gender				
Male	0.00		0.00	
Female	-0.01 (-0.09, 0.07)	*p=0.790*	-0.01 (-0.07, 0.06)	*p=0.891*
Maternal ethnicity				
White	0.00		0.00	
Black	0.49 (0.41, 0.58)	*p<0.001*	0.27 (0.17, 0.36)	*p<0.001*
Other	0.15 (-0.02, 0.32)	*p=0.077*	0.04 (-0.11, 0.20)	*p=0.607*
Maternal illicit drug use				
Never	0.00		0.00	
Past user/user timing unknown	-0.41 (-0.50, -0.32)	*p<0.001*	-0.29 (-0.39, -0.20)	*p<0.001*
Current	-0.67 (-0.77, -0.56)	*p<0.001*	-0.51 (-0.62, -0.40)	*p<0.001*

*Adjusted for all other variables in model.
The univariable and multivariable coefficient included 1745 mother-child pairs.
CI, confidence interval.

Table 5.4 Length/height (z-score) and maternal and infant factors in the first 18 months of life

	Unadjusted coefficient (95% CI)	*p value*	Adjusted coefficient* (95% CI)	*p value*
Antenatal ART exposure				
None/monotherapy	0.00		0.00	
Combination therapy	0.01 (-0.08, 0.10)	*p=0.903*	-0.12 (-0.21, -0.03)	*p=0.008*
Gestational age (weeks)				
≥ 37	0.00		0.00	
34-36	-0.63 (-0.74, -0.51)	*p<0.001*	-0.58 (-0.69, -0.47)	*p<0.001*
<34	-1.32 (-1.52, -1.12)	*p<0.001*	-1.26 (-1.45, -1.07)	*p<0.001*
Gender				
Male	0.00		0.00	
Female	-0.02 (-0.11, 0.06)	*p=0.577*	-0.02 (-0.09, 0.06)	*p=0.690*
Maternal ethnicity				
White	0.00		0.00	
Black	0.36 (0.27, 0.45)	*p<0.001*	0.17 (0.07, 0.27)	*p=0.001*
Other	0.04 (-0.14, 0.23)	*p=0.648*	-0.03 (-0.20, 0.15)	*p=0.756*
Maternal illicit drug use				
Never	0.00		0.00	
Past user/user timing unknown	-0.30 (-0.39, -0.20)	*p<0.001*	-0.24 (-0.35, -0.13)	*p<0.001*
Current	-0.56 (-0.68, -0.45)	*p<0.001*	-0.48 (-0.61, -0.36)	*p<0.001*

*Adjusted for all other variables in model.
The univariable and multivariable coefficient included 1638 mother-child pairs.
CI, confidence interval.

Table 5.5 Head circumference (z-score) and maternal and infant factors in the first 18 months of life

	Unadjusted coefficient (95% CI)	*p value*	Adjusted coefficient* (95% CI)	*p value*
Antenatal ART exposure				
None/monotherapy	0.00		0.00	
Combination therapy	0.02 (-0.07, 0.10)	*p=0.709*	-0.14 (-0.23, -0.06)	*p=0.001*
Gestational age (weeks)				
≥ 37	0.00		0.00	
34-36	-0.63 (-0.73, -0.52)	*p<0.001*	-0.57 (-0.68, -0.47)	*p<0.001*
<34	-1.39 (-1.58, -1.20)	*p<0.001*	-1.33 (-1.51, -1.15)	*p<0.001*
Gender				
Male	0.00		0.00	
Female	-0.04 (-0.12, 0.05)	*p=0.402*	-0.04 (-0.11, 0.04)	*p=0.340*
Maternal ethnicity				
White	0.00		0.00	
Black	0.50 (0.41, 0.58)	*p<0.001*	0.33 (0.24, 0.43)	*p<0.001*
Other	0.16 (-0.02, 0.33)	*p=0.078*	0.09 (-0.07, 0.26)	*p=0.266*
Maternal illicit drug use				
Never	0.00		0.00	
Past user/user timing unknown	-0.38 (-0.48, -0.29)	*p<0.001*	-0.24 (-0.34, -0.14)	*p<0.001*
Current	-0.57 (-0.68, -0.46)	*p<0.001*	-0.41 (-0.52, -0.29)	*p<0.001*

*Adjusted for all other variables in model.
The univariable and multivariable coefficient included 1707 mother-child pairs.
CI, confidence interval.

Adjusting for unobserved variation between centres by inclusion of a random effects variable at centre level did improve the fit of the weight, length/height and OFC models, although the coefficients in Tables 5.3-5.5 remained of a similar magnitude.

Adjusted coefficients for explanatory variables were broadly similar for all three growth measurements (Tables 5.3-5.5) suggesting they were internally consistent within child. To investigate this consistency further, sub-analyses were conducted where length/height categorised as z-score quartiles was added as an explanatory variable in the weight model, weight in the length/height model, and weight in the OFC model. This significantly improved the fit of each model ($p<0.001$). In the model for weight, children who were taller than the baseline were also heavier. This was also the case in the models for length/height and OFC.

In additional sub-analyses of mother-child pairs with available information, maternal CD4 cell count was not significantly associated with weight (705 mother-child pairs), length/height (669 mother-child pairs) or OFC (687 mother-child pairs) in univariable or multivariable models when adjusting for antenatal ART exposure, gestational age, gender, maternal ethnicity and IDU. Inclusion of CD4 cell count did not improve the fit of any of the models (weight $p=0.712$, length/height $p=0.682$ or OFC $p=0.356$) and the coefficients did not alter substantially.

5.4 Key points

- for term children or children born before 34 weeks, weight and OFC at birth did not differ between those with no or monotherapy exposure and those with combination therapy exposure; children born at 34-36 weeks with combination therapy exposure were heavier and had a larger OFC than children born at 34-36 weeks with no or monotherapy exposure
- children born at 34-36 weeks exposed to combination therapy reached the 25th centile for weight and OFC earlier than those born at 34-36 weeks with no or

monotherapy exposure (median age: birth versus three months for both weight and OFC)

- children born before 34 weeks exposed to combination therapy reached the 25th centile for OFC later than those born before 34 weeks with no or monotherapy exposure (median age: fifteen months versus seven months); for all children born before 34 weeks, the estimated median age at reaching the 25th centile for weight was over a year regardless of exposure
- when adjusting for gestational age, gender, maternal ethnicity and maternal IDU, there was a marginal but significant negative effect of combination therapy exposure on growth up to 18 months of age when compared with no or monotherapy exposure (adjusted coefficients: -0.10 for weight ($p=0.019$), -0.12 for length/height ($p=0.008$) and -0.14 for OFC ($p=0.001$))

Chapter 6 The Office for National Statistics flagging study

"When the baby is healthy and doesn't have any problems she doesn't need to be coming to the hospital. She's doing well but you never know if she will get a problem."

[Mother of one child (aged 3 months)]

"Personally I find it difficult to allocate outpatient slots as I am seeing these patients in the context of a busy neonatal follow up programme and as patient numbers increase this problem will escalate. A non clinic contact is therefore attractive."

[Paediatrician]

6.1 Introduction

The carcinogenic potential of transplacental zidovudine (ZDV) exposure has been demonstrated in animal studies (Olivero *et al.* 1997, Olivero *et al.* 2002). Although ZDV exposure has not been reported to be associated with cancer in early childhood (Culnane *et al.* 1999, Hanson *et al.* 1999), the possibility of development of cancer later on in life remains.

The UK Office for National Statistics (ONS) provides a resource whereby medical researchers are able to monitor death and cancer among subjects in their study. Subjects are identified on the National Health Service Central Register (NHSCR) and their records are marked with a study number ("flagged"). Details of death and cancer registration in the subjects are then supplied to the researchers (Greenberg and Coleman 2000).

A protocol was established for flagging children reported to the National Study of HIV in Pregnancy and Childhood (NSHPC) to obtain notifications of death and cancer registration over the long term. This was done through an automatic matching procedure on the Births/Deaths Registration Database (BDRD) at the General Register Office (GRO). By the end of 2005, the majority of children reported to the NSHPC born in England and Wales 2001-2004 had been flagged. Details on the methods of the NSHPC and flagging studies are provided in Sections 2.2 and 2.4 respectively.

6.2 Development of a protocol for flagging

6.2.1 Matching algorithm

Birth registration records of children reported to the NSHPC were identified on the BDRD using a set of criteria ("matching algorithm"). A test dataset using the records of

179 children reported to the NSHPC was used in the development of the matching algorithm (Table 6.1).

Table 6.1 Information available for the test dataset children (n=179)

Variable	Children with information available from NSHPC database n (%)
Child's NHS number	179 (100)
Child's date of birth	179 (100)
Child's sex	178 (99)
Mother's date of birth	175 (98)
Mother's postcode district* of residence at delivery	163 (91)
Child's birth weight	145 (81)
Mother's country of birth	130 (73)

Notes
*postcode district is the first half of a postcode e.g. A12 is the postcode district of A12 3BC
NSHPC, National Study of HIV in Pregnancy and Childhood; NHS, National Health Service
The test dataset children were born in England and Wales 1998-2004 and reported to the NSHPC by June 2004.

The general structure of the algorithm was a hierarchical set of match types, each one consisting of one or more variables. For each study subject, variables according to those in the first match type were compared with the BDRD to see if the subject matched with any birth registration records. If a match for the subject was not made, the second match type was used, and so on, until either a match was made or the end of the algorithm was reached. The aim in selecting match types for the algorithm was to maximise the number of subjects where a unique correct match with a birth registration record was made, and to minimise the number of subjects where incorrect or multiple matches were made.

Variables both in the NSHPC database and the BDRD that were suitable for use in the algorithm were: child's National Health Service (NHS) number, date of birth and sex;

and mother's date of birth and postcode district of residence at delivery (postcode district is the first half of a postcode, e.g. A12 is the postcode district of A12 3BC).

Child's birth weight, mother's country of birth and the variables used in the algorithm (see previous paragraph) were provided for the matches made using the algorithm (output dataset). For the purposes of selecting match types for the algorithm, matches were considered correct if they agreed on at least one of the following not in the relevant match type: child's birth weight, mother's date of birth, mother's postcode district of residence at delivery or mother's country of birth; and incorrect if they did not agree on any. The finalised algorithm is shown in Table 6.2.

Table 6.2 The matching algorithm used in the Office for National Statistics flagging study

Match type 1) Child's date of birth, sex and NHS number
Match type 2) Child's date of birth, sex and mother's date of birth
Match type 3) Child's date of birth and mother's date of birth
Match type 4) Child's date of birth, sex and mother's postcode district of residence at delivery
Match type 5) Mother's date of birth, sex and mother's postcode district of residence at delivery
Match type 6) NHS number

NHS, National Health Service

When the finalised algorithm was used on the test dataset, 166 (93%) of the 179 subjects were matched uniquely and correctly on type 1. Eight subjects were matched uniquely and correctly on type 2, one on type 4, one on type 5 and one on type 6. Two matches were made for one subject on type 2 and two for one subject on type 3; and for both the correct match could be identified.

Several observations were made in the development of the algorithm. A match type with child's date of birth, sex and NHS number (match type 1) was effective at making unique correct matches for subjects. However, despite all subjects in the test dataset having an NHS number recorded, 7% (13/179) of subjects were not matched on type 1. This was because data was missing or did not match between the NSHPC database and the BDRD. A match type consisting of only NHS number was important if mother's date of birth and child's date of birth were either missing or did not match between the databases. However, this match type was only used at the end of the algorithm as an error in NHS number would be less likely to lead to an incorrect match at that stage than if it was near the beginning. If a subject was a twin and was not matched on type 1 but there were multiple matches on another match type that included its sibling, birth weight had to be used to identify the correct match.

6.2.2 Confirmation of matches made using matching algorithm

Introduction

NHS number was not available for all children reported to the NSHPC. To assess whether matches made using the algorithm without NHS number would be the same as those made with NHS number, the algorithm was used on the test dataset with NHS number excluded. As NHS number was provided in the output dataset, matches made without NHS number could be compared with those made with it. Matches were identified as correct if NHS number was the same; and incorrect if it was different. This exercise only applied to the 166 subjects that matched on type 1 with NHS number (see Appendices 4.1 and 4.2).

Unique matches

Of the 166 subjects that were matched on type 1 with NHS number, without NHS number 121 (121/166, 73%) were matched uniquely and correctly on type 2 and five (5/166, 3%) on type 4. However, seven (7/166, 4%) subjects were matched uniquely and incorrectly on type 2, 3 or 4 (Appendix 4.1).

Of the 126 subjects that were matched uniquely and correctly on type 2 or 4, 125 also agreed on at least one of: child's birth weight (within 10g), mother's country of birth or mother's postcode district of residence at delivery (the latter not included for type 4). However, of the seven subjects that were matched uniquely and incorrectly on type 2, 3 or 4, all disagreed on at least one of the above three variables. Only one of the seven subjects agreed on any of them (mother's postcode district of residence at delivery not included for type 4), and in this case mother's country of birth was the UK (Appendix 4.1).

No matches

One subject had no match, and this was because mother's date of birth and mother's postcode district of residence at delivery were missing in the test dataset (Appendix 4.1).

Multiple matches

Thirty two (32/166, 19%) subjects had multiple matches on either type 2 or type 4. These included the correct match for 30 subjects (Appendix 4.2). Correct and incorrect matches for the 32 subjects could generally be related to how many variables they agreed or disagreed on, of: child's birth weight (within 10g), mother's country of birth or mother's postcode district of residence at delivery (the latter not included for type 4). However for four subjects, incorrect matches agreed on mother's country of birth when it was the UK,

and therefore there had to be agreement on another variable to distinguish correct from incorrect. For twin pairs, the correct match had to agree on child's birth weight for it to be distinguished from the incorrect match (i.e. its sibling) (2 subjects). For one subject the correct match could not be distinguished from incorrect (Appendix 4.2).

Confirmation of matches

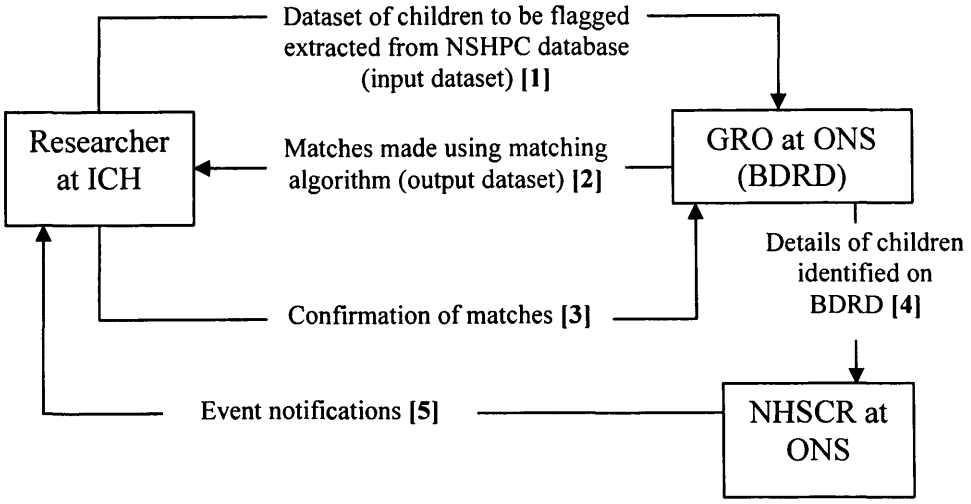
If subjects that were matched uniquely without NHS number had then been flagged without any further confirmation, 5% (7/133) of them would have been flagged incorrectly. Furthermore, a relatively high proportion of the 166 subjects had multiple matches (32/166, 19%).

A stage was therefore built into the protocol to confirm non-type 1 matches made using the algorithm, determined by the agreement in the test dataset of: child's birth weight (within 10g), mother's country of birth and mother's postcode district of residence at delivery (Appendices 4.1 and 4.2). A programme was written in SAS (SAS statistical software, version 8.02, SAS Institute, Cary, North Carolina, USA) for this confirmation, according to the criteria outlined in Appendix 4.3.

6.2.3 Protocol for flagging

The protocol established for flagging children reported to the NSHPC on the NHSCR for notifications of death and cancer registration over the long term, is shown in Figure 6.1. See Section 2.4 for the general methodology of flagging studies.

Figure 6.1 Protocol for flagging children reported to the National Study of HIV in Pregnancy and Childhood on the National Health Service Central Register



Notes: GRO, General Register Office; NHSCR; National Health Service Central Register; ICH, Institute of Child Health; NSHPC, National Study of HIV in Pregnancy and Childhood; ONS, Office for National Statistics; BDRD, Births/Deaths Registration Database

6.3 Inclusion criteria for flagging children reported to the National Study of HIV in Pregnancy and Childhood (2005)

Data presented here relate to children reported to the NSHPC by June 2005. The inclusion criteria for the ONS flagging study in 2005 were children reported to the NSHPC who were:

- born in England or Wales 2001-2004 and
- of any HIV infection status and
- of any ART exposure

The restriction was made on country of birth as the BDRD only includes births registered in England and Wales. Children were included regardless of reported HIV infection status as:

- for indeterminate children, the majority are likely to have been exposed to ART; and once confirmation of infection status is reported to the NSHPC, the majority are likely to be uninfected
- for infected children, notifications of death and cancer registration reported from ONS enable clarification of information reported to the NSHPC through annual follow-up (see Section 2.2)

Children were included regardless of reported ART exposure as forms sent to the NSHPC at a later date could provide additional information about ART exposure (Appendix 3).

By June 2005 there were 2842 children who met the inclusion criteria for flagging (Table 6.3). Of these, 2040 (72%) were uninfected, 85 (3%) were infected and 717 (25%) were of indeterminate status. Of the indeterminate children, 707 (707/717, 99%) were born to women diagnosed with HIV infection before delivery. The majority of children were born in England (2815/2842, 99%). A total of 2135 (2135/2842, 75%) children had been reported through both the obstetric and paediatric reporting schemes, 481 through obstetric only and 226 through paediatric only.

Table 6.3 Children born in England and Wales and reported to the National Study of HIV in Pregnancy and Childhood

Year of birth	Children reported by June 2005 (n)	Children with National Health Service (NHS) number supplied n (%)
2001	483	202 (42)
2002	606	334 (55)
2003	850	610 (72)
2004	903	658 (73)

6.4 Flagging of children reported to the National Study of HIV in Pregnancy and Childhood (2005)

6.4.1 Input dataset

A dataset on the 2842 children who met the inclusion criteria for flagging was extracted from the NSHPC database. This consisted of the variables in Table 6.4 as well as NSHPC study number and whether the child was a singleton or from a multiple birth. The dataset was checked for data inconsistencies; original forms were consulted and NSHPC respondents contacted for clarification as appropriate.

6.4.2 Output dataset

When the algorithm (see Table 6.2) was used on the input dataset, 1739 (1739/2842, 61%) of the 2842 children who met the inclusion criteria for flagging were matched on type 1. A third (892/2842, 31%) of children were matched uniquely on types 2-6, 6% (179/2842) of children had multiple matches on types 2-5 and 1% (32/2842) had no match (see column [1] on Table 6.5).

Table 6.4 Information available for children to be flagged (n=2842)

Variable	Children with information available from the NSHPC database n (%)
NHS number	1804 (63)
Date of birth	2842 (100)
Sex	2822 (99)
Birth weight*	1853 (65)
Mother's date of birth	2800 (99)
Mother's postcode district of residence at delivery	2769 (97)
Mother's country of birth*	2706 (95)

*Not used in matching algorithm
NSHPC, National Study of HIV in Pregnancy and Childhood; NHS, National Health Service

Table 6.5 Matching algorithm, confirmation of matches and flagging

Match type and number of matches made using algorithm	[1] Children with type and number of matches made using algorithm n (%)	[2] Children with confirmation of match n	[3] Details sent to NHSCR n	[4] Children flagged n (%)
Type 1: *unique*	1739 (61)	-	1739*	1738 (65)
Type 2: *unique*	793 (28)	762	762*	759 (28)
Type 2: *2 matches*	96 (3)	82	82	82 (3)
Type 2: *3 matches*	10 (<1)	8	8	8 (<1)
Type 2: *4 matches*	2 (<1)	1	1	1 (<1)
Type 3: *unique*	33 (1)	16	16	16 (1)
Type 3: *2 matches*	8 (<1)	6	6	6 (<1)
Type 4: *unique*	56 (2)	29	29*	28 (1)
Type 4: *2 matches*	35 (1)	27	27	27 (1)
Type 4: *3 matches*	14 (<1)	10	10	10 (<1)
Type 4: *4 matches*	8 (<1)	6	6	6 (<1)
Type 4: *6 matches*	1 (<1)	1	1	1 (<1)
Type 4: *7 matches*	1 (<1)	1	1	1 (<1)
Type 5: *unique*	8 (<1)	6	6	6 (<1)
Type 5: *2 matches*	4 (<1)	2	2	2 (<1)
Type 6: *unique*	2 (<1)	2	2	2 (<1)
No match	32 (1)	-	0	0 (0)
Total	**2842 (100)**	*959*	**2698**	**2693 (100)**

* Five children could not be flagged (see Section 6.4.4). NHSCR, National Health Service Central Register

6.4.3 Confirmation of matches

The confirmation of matches programme was used on non-type 1 matches from the output dataset (see Appendix 4.3). Of the 892 children who were matched uniquely on types 2-6, 815 (91%) met the confirmation criteria; and of the 179 children who had multiple matches on types 2-5, 144 (80%) had a match that met the confirmation criteria (see column [2] on Table 6.5).

6.4.4 Flagging

Details on the 959 children who met the confirmation criteria, plus the 1739 children who were matched on type 1, were obtained from the BDRD and were sent to the NHSCR (see column [3] on Table 6.5) (Figure 6.1).

There were five children who could not be flagged as their records on the NHSCR had been closed. This occurs in various situations, e.g. adoption. In total, 2693 (2693/2842, 95%) of the 2842 children who met the inclusion criteria for flagging were flagged on the NHSCR (see column [4] on Table 6.5).

6.4.5 Characteristics of flagged and non-flagged children

Flagged and non-flagged children were compared in terms of the characteristics shown in Table 6.6. Univariable comparisons were tested with χ^2 tests.

There was a significant increase in the proportion of children flagged by year of birth from 2001 to 2004 (p=0.004), which is likely to be due to the increased availability of NHS number (see Table 6.3). There was no significant difference between children who were flagged and those who were not, in terms of antenatal ART exposure (p=0.452), gestational age (p=0.294) or maternal area of birth (p=0.663).

Table 6.6 Characteristics of flagged and non-flagged children (n=2842)

	Flagged n (%)	Non-flagged n (%)	χ^2 p value
Year of birth (n=2842)			
2001	443 (16)	40 (27)	
2002	571 (21)	35 (23)	
2003	811 (30)	39 (26)	
2004	868 (32)	35 (23)	χ^2, 13.45, p=0.004
Maternal area of birth (n=2790)			
Europe	377 (14)	19 (13)	
Sub-Saharan Africa	2095 (79)	117 (82)	
Other	175 (7)	7 (5)	χ^2, 0.82, p=0.663
Gestational age (n=2765)			
$\geq$ 37 weeks	2237 (85)	113 (82)	
< 37 weeks	390 (15)	25 (18)	χ^2, 1.10, p=0.294
Antenatal antiretroviral therapy exposure (n=2782)			
None	173 (7)	13 (9)	
Monotherapy	441 (17)	23 (16)	
Double therapy	55 (2)	1 (1)	
3 or more drugs	1970 (75)	106 (74)	χ^2, 2.63, p=0.452

Note: data reported to the National Study of HIV in Pregnancy and Childhood by the end of 2005

6.5 Notifications of death and cancer registration in flagged uninfected children by the end of 2005

6.5.1 Children born before 2001

As outlined in Section 2.4, 329 children reported to the NSHPC born 1996-1999 were flagged on the NHSCR in the late 1990s. A further 24 children born 1998-2000 were flagged in 2005 during the development of the matching algorithm. Of the 353 children, 79 (22%) were infected, 29 (8%) indeterminate and 245 (69%) uninfected.

For the 245 uninfected children, total length of time on the NHSCR and therefore opportunity for death or cancer registration to be reported, by the end of 2005 was 2033

child-years: 1578 child-years (median 8.1 years, range 5.0-10.0) in 194 children exposed to antenatal ART and 455 child-years (median 9.3 years, range 5.4-10.0) in 51 children not exposed to antenatal ART (n=37) or with missing exposure information (n=14). No notifications of death or cancer registration had been reported from ONS by the end of 2005.

6.5.2 Children born 2001-2004

Of the 2693 children flagged in 2005, 81 (3%) were reported to be infected, 428 (16%) indeterminate and 2184 (81%) uninfected by the end of 2005.

Total length of time on the NHSCR for the 2184 uninfected children by the end of 2005 was 6023 child-years: 5732 child-years (median 2.6 years, range 1.0-5.0) in 2085 children exposed to antenatal ART and 291 child-years (median 2.9 years, range 1.1-4.9) in 99 children not exposed to antenatal ART (n=82) or with missing exposure information (n=17).

No notifications of cancer registration had been reported from ONS by the end of 2005. There had been three death registrations reported from ONS by the end of 2005 (Table 6.7), two of which had already been reported to the NSHPC by respondents. No child had evidence of cancer in their death registration.

Table 6.7 Notifications of death registration in flagged uninfected children born 2001-2004

Child	Antiretroviral therapy exposure	Gestational age (weeks)	Congenital abnormality reported to NSHPC? (System)	Cause of death	Age at death
1	Antenatal: ZDV + 3TC + NVP Intrapartum: Missing Neonatal: ZDV	40	Yes (Circulatory)	Congenital heart disease	8 months
2	None	39	No	Congenital malformation of respiratory system	9 months
3	Antenatal: ZDV + 3TC + NVP Intrapartum: ZDV Neonatal: ZDV	26	No	Tuberculosis	1 month

ZDV, zidovudine; 3TC, lamivudine; NVP, nevirapine; NSHPC, National Study of HIV in Pregnancy and Childhood

6.6 Key points

- a protocol was established to flag children reported to the NSHPC on the NHSCR for notifications of death and cancer registration
- the protocol included: a matching algorithm used to identify birth registration records on the BDRD and a programme used to confirm matches
- variables used in the matching algorithm were: child's date of birth, sex and NHS number; and mother's date of birth and postcode district of residence at delivery
- although NHS number was important in the identification of birth registration records, they could still be identified without it
- 95% of children reported to the NSHPC born in England and Wales 2001-2004, had been flagged by the end of 2005
- there was no significant difference in antenatal ART exposure between children who were flagged and those who were not
- by the end of 2005, 2429 uninfected children reported to the NSHPC had been flagged: 245 born 1996-2000 and 2184 born 2001-2004
- total length of time on the NHSCR for the 2429 uninfected children was 8056 child-years
- by the end of 2005, there had been no notifications of cancer registration and three notifications of death registration in uninfected children

Chapter 7 Follow up of uninfected children born to HIV infected women in the UK: the CHART study

"I think it is a good idea following up these children because it shows you have their interest at heart and would like to know and help them if they do get any side effects from the drugs."

[Mother of two children (aged 1 and 7 years)]

"Although I strongly support research into the follow-up of children exposed to anti HIV drugs I am currently unwilling to give my permission for this to happen as I feel that my decision of when or whether to tell my child about my HIV status could be taken out of my hands. If you can assure me this won't happen I will happily comply."

[Mother of one child (aged 1 year)]

"People do not think through what it means- i.e. they do want to help/be followed up but change address, phones etc and CHART is not on their minds once they move on with children growing up. I have never spoken to anyone who didn't think it important in principle; it's the intrusion in their lives which puts them off."

[Paediatric nurse]

7.1 Introduction

The prevalence of HIV infection in pregnant women in the UK has increased in recent years, as have detection rates. In 2004 the prevalence of HIV among women giving birth in England and Scotland was 0.18%, and approximately 90% of HIV infected pregnant women were diagnosed prior to delivery (The UK Collaborative Group for HIV and STI Surveillance 2005). Interventions to reduce mother-to-child transmission (MTCT) have meant that MTCT rates have decreased to around 2% (European Collaborative Study 2005c, Duong *et al.* 1999). These factors have resulted in a substantial increase in the number of uninfected children born to HIV infected women in the UK. By the end of 2004, the National Study of HIV in Pregnancy and Childhood (NSHPC) had recorded 291 born in 2000, 398 in 2001, 493 in 2002 and 593 in 2003. In 2005 over 95% of HIV infected pregnant women reported to the NSHPC were on antiretroviral therapy (ART) (Tookey 2005b).

The CHART study, a consented annual clinic-based follow-up of uninfected children born to HIV infected women in the UK and reported to the NSHPC, was conducted to explore the feasibility of individualised follow-up to monitor adverse health events that could be related to ART exposure in fetal and/or early life. Enrolment in the CHART study is described in this chapter. Results from a survey among health professionals on their clinic practice regarding uninfected children and experiences with the CHART study, are also presented (see Section 2.6).

7.2 Methods

The initial approach for follow-up information on an eligible child was made through the NSHPC paediatric respondent after the child's infection status was reported. If it was more appropriate, an alternative health professional aware of the mother's HIV infection

status was contacted, e.g. genitourinary (GU) physician, general practitioner (GP), health visitor. Health professionals were reminded on a regular basis about children whose enrolment status had not been confirmed. Parental consent was sought for enrolment, and an annual questionnaire on the child's health and development was completed opportunistically by the health professional with the parent or carer. Demographic, perinatal and ART exposure information was prospectively collected through the NSHPC. Further details on the CHART study and the NSHPC are provided in Chapter 2.

Eligibility for enrolment in the CHART study

Children were eligible for enrolment in the CHART study if they were uninfected (see Appendix 3.3 for definition), born in the UK to HIV infected women diagnosed before delivery, reported to the NSHPC by March 2005 and:

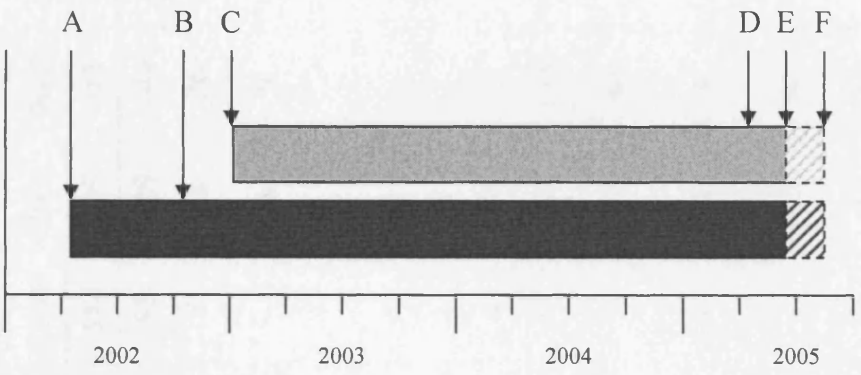
- reported from a "core" hospital (see below) and born between January 1996 and December 2000 **OR**
- reported from any hospital in the UK and born between January 2001 and April 2004

Time scale of the CHART study

The CHART study was carried out between 2002 and 2005. Enrolment of uninfected children born since 1996 started in five hospitals in London in April 2002, and then in six hospitals in Oxford, Sheffield, Leicester, Birmingham and London (2 hospitals) in October 2002 (core hospitals) (see Figure 7.1 and Appendix 5). The core hospitals were selected on the basis of number of reports made to the NSHPC and hospital location. Just under half (334/777, 43%) of all uninfected children born in the UK to HIV infected women between 1996 and 2000, were reported from the 11 core hospitals. In January 2003, the CHART study was extended to include uninfected children born since 2001 and reported from any hospital in the UK (Figure 7.1). In April 2005, all health

professionals who had been approached regarding enrolment of a child, and from whom no reply had been received, were contacted again and asked to provide information on the child's enrolment status (e.g. enrolled, declined, lost to follow-up, could not enrol before end of study period etc). Study enrolment ceased in June 2005 and data collection ceased in August 2005.

Figure 7.1 Time scale of the CHART study



Notes

Uninfected children born 1996-April 2004 reported to NSHPC by March 2005 from 11 core hospitals

Uninfected children born 2001-April 2004 reported to NSHPC by March 2005 from non-core hospitals

A=Enrolment started in 5 first phase core hospitals (April 2002)
B=Enrolment started in 6 second phase core hospitals (October 2002)
C=Enrolment started in non-core hospitals (January 2003)
D=Status clarification (April 2005)
E=End of study enrolment (June 2005)
F=End of data collection (August 2005)

7.3 Enrolment in the CHART study

A total of 2104 children were eligible for enrolment in the CHART study (Table 7.1). Of these, 334 were born between 1996 and 2000 and reported to the NSHPC from the 11 core hospitals (median number of reports per hospital was 13, range 5-64). The remaining 1770 eligible children were born between January 2001 and April 2004 and reported from 168 hospitals in the UK (median number of reports per hospital was 3, range 1-125).

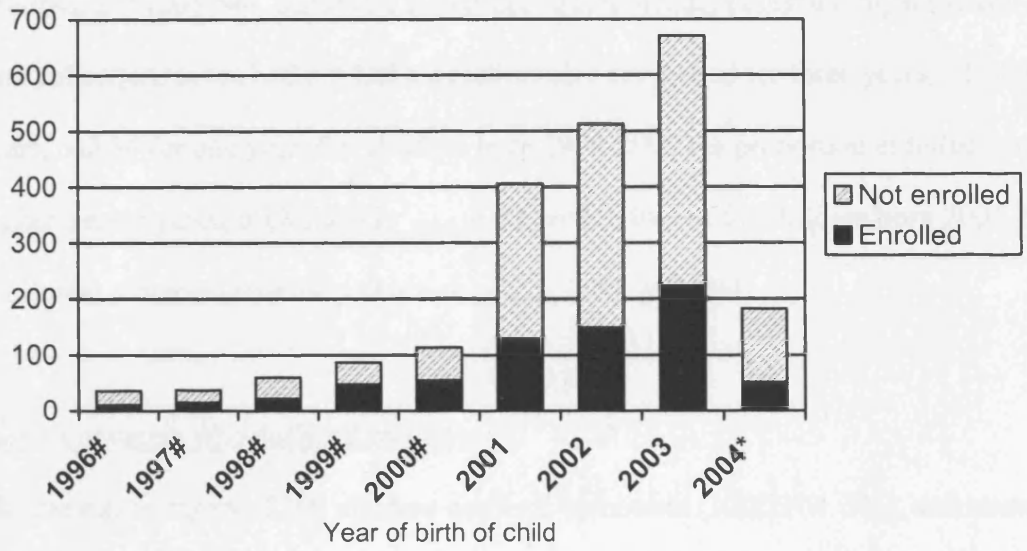
Table 7.1 Enrolment in the CHART study: April 2002-June 2005

	Year of birth of child									Total
	1996*	1997*	1998*	1999*	2000*	2001	2002	2003	2004β	n (%)#
Children eligible for CHART study	**36**	**37**	**60**	**87**	**114**	**405**	**512**	**670**	**183**	**2104**
Child enrolled	11	15	22	48	55	129	149	224	51	704 (33)
Child's parent/carer declined enrolment	2	2	4	4	7	18	26	33	4	100 (5)
Health professional decided it inappropriate to approach parent/carer	-	-	-	-	-	4	9	5	1	19 (1)
Child died	-	1	-	-	-	-	-	1	-	2 (<1)
Child's mother died- no access to child	-	2	1	1	-	1	-	-	-	5 (<1)
Child fostered/adopted- no access to child	-	1	-	-	1	1	2	1	-	6 (<1)
Child left the UK	1	1	3	3	4	10	17	16	4	59 (3)
Child lost to follow-up	19	14	24	24	35	107	118	102	12	455 (22)
Health professional unable to contact family before end of CHART study	2	1	3	3	9	27	42	96	50	233 (11)
Health professional could not identify child from case identifiers provided	1	-	1	-	-	4	4	3	1	14 (<1)
Health professional unable to participate in CHART study	-	-	-	-	-	47	62	95	26	230 (11)
No response from health professional	-	-	2	4	3	57	83	94	34	277 (13)

*Children reported from the core hospitals (see Appendix 5). NSHPC, National Study of HIV in Pregnancy and Childhood. #Percentage of eligible children. βBorn January-April 2004.

At the end of study enrolment in June 2005, 704 (33%) of the 2104 eligible children had been enrolled: 151 born 1996-2000 and 553 born 2001-2004 (Table 7.1 and Figure 7.2). Though the number of eligible children increased over the study period, the proportion enrolled also increased: 21% (89/424) at the end of 2002 (core hospitals only), 23% (262/1128) at the end of 2003 and 26% (514/1958) at the end of 2004.

Figure 7.2 Children eligible for the CHART study by enrolment status (n=2104)



Data at the end of June 2005
*born January-April 2004. #reported from the 11 core hospitals (see Appendix 5).

Overall, parents or carers of 5% (100/2104) of children declined enrolment (Table 7.1), thus of the parents and carers approached regarding enrolment, 88% (704/804) agreed to take part. A further 22% (455/2104) were reported to be lost to follow-up and 3% (59/2104) were known to have left the UK. Two children were reported to have died (one of sudden infant death syndrome (SIDS) and one of tuberculosis). The remaining 37% (784/2104) of children could not be enrolled because they had been reported from a hospital unable to participate in the CHART study (n=230), the health professional had

not been able to access the family (timing issues, could not identify child, inappropriate to approach family about study, child fostered or adopted, mother had died) (n=277), or there had been no response from the health professional despite reminders (n=277).

Enrolled children

Of the 704 enrolled children, 47 (7%) were subsequently reported as lost to follow-up, and the parents or carers of 13 (2%) declined further follow-up. Of the remaining children, 203 (203/644, 32%) had subsequent questionnaires outstanding at the end of data collection: seven had not had a questionnaire completed for three years, 112 for two years, and 84 for one year. For children born 1996-2000 the proportion enrolled was higher among younger children (χ^2_{trend}, 4.72, p=0.030), but for children born 2001-2004 enrolment remained relatively constant (χ^2_{trend}, 0.00, p=0.994).

Parents or carers who declined enrolment

The parents or carers of 100 children declined enrolment (100/2104, 5%), and reasons were provided by health professionals for 38 of them (Table 7.2).

Table 7.2 Reasons for child's parent/carer declining enrolment in the CHART study (n=38)

Reason	n
Issues with confidentiality*	14
Issues with acceptance of HIV diagnosis / does not want to be reminded of HIV diagnosis	9
Logistical reasons (too far to travel / leaving the UK)	4
Child well	2
Does not want further appointments for the child	5
Lack of time	4

* included: concern that either family members or their partner would find out about their HIV diagnosis, not wanting information on their child to leave the hospital, not being willing to talk about HIV over the telephone

Loss to follow-up

Of the 22% (455/2104) of eligible children reported as lost to follow-up, reasons were provided by health professionals for half of them (Table 7.3). Health professionals reported 46 children as lost to follow-up because they had been discharged from the paediatric clinic; no contact details of alternative health professionals had been provided.

Table 7.3 Reasons for loss to follow-up of children eligible for the CHART study (n=221)

Reason	n
Clinic non-attendance (paediatric/genitourinary clinic)	72
Family moved / contact details held by clinic not current / no longer registered at GP practice	103
Child discharged from paediatric clinic	46

Participation of health professionals

Contacts

During the study period, 335 health professionals were contacted regarding study enrolment and data collection (Table 7.4). Alternative health professionals (i.e. not NSHPC paediatric respondents) were contacted regarding the enrolment of 135 children (35 were then enrolled); and the completion of subsequent questionnaires for 27 children (seven were then completed).

Health professionals unable to participate

Health professionals from 11 hospitals and general practices reported they were unable to participate in the CHART study, which meant that 11% (230/2104) of eligible children could not be enrolled (Table 7.1). Lack of resources was generally cited as a reason.

Table 7.4 Health professionals contacted regarding enrolment of children in the CHART study

	n (%)
Paediatrician	188 (56)
Community paediatrician	3 (1)
Nurse (paediatrics)	22 (7)
GU physician	40 (12)
Nurse (GU medicine)	13 (4)
Midwife	4 (1)
Health visitor	6 (2)
GP	59 (18)
Total	**335**

GU, genitourinary

Health professional decided it inappropriate to approach the family about the study

Health professionals contacted regarding the enrolment of 19 children, reported that it would be inappropriate to approach the family about the study. Reasons given included: health of the mother, issues with HIV diagnosis, confidentiality, and previous difficulties with testing or treating the child.

7.4 Characteristics of children eligible for the CHART study

Of the 1770 eligible children born 2001-2004, 76% (1322/1741) were born to women from sub-Saharan Africa, with 17% (289/1741) born to women from Europe. In terms of maternal HIV risk factor, injecting drug use was reported for the mothers of 2% (32/1671) of children, whereas being from an HIV high-prevalence area was reported for 87% (1453/1671). Median maternal age at delivery was 29.8 years (range 14.5-53.3). A total of 96% (1687/1755) of children had been exposed to antenatal ART, mostly combination therapy (n=1358).

The 334 eligible children born 1996-2000 and reported from the 11 core hospitals had similar demographic characteristics to the younger children: 74% (244/328) were born to women from sub-Saharan Africa and 21% (69/328) born to women from Europe. Injecting drug use was reported for the mothers of 6% (21/327) of children, and being from a high-prevalence area was reported for 80% (260/327). Median maternal age at delivery was 30.1 years (range 17.4-41.4). A total of 89% (294/330) of children had been exposed to antenatal ART.

Characteristics of eligible children by enrolment status

Characteristics of eligible children, according to whether or not they were enrolled in the CHART study, are shown in Table 7.5. Enrolled children and non-enrolled children were similar in terms of maternal HIV risk factor (p=0.248), maternal area of birth (p=0.389) and gestational age (p=0.448) (Table 7.5). However enrolled children were more likely to have an older mother than those who were not enrolled (p=0.003); and enrolled children were more likely to have been exposed to antenatal ART (674/697, 97%) than non-enrolled children (1297/1378, 94%) (χ^2, 6.46, p=0.011).

Children whose parents or carers declined enrolment were less likely to have been exposed to antenatal ART (89/98, 91%), than those whose agreed to enrolment (674/697, 97%) (χ^2, 7.70, p=0.006); there were no differences in terms of demographic characteristics.

Age at last contact

Median age at last contact for the non-enrolled children (reported on NSHPC paediatric forms) was 6 months (range 1-45). Median age at last contact for the enrolled children, reported through the CHART study, was 24 months (range 5-106).

Table 7.5 Characteristics of eligible children by enrolment status (n=2104)

	Enrolled n (%)	Non-enrolled n (%)	χ^2 p value
Maternal area of birth (n=2069)			
Europe	115 (16)	243 (18)	
Sub-Saharan Africa	540 (77)	1026 (75)	
Other	43 (6)	102 (7)	χ^2, 1.89, p=0.389
Maternal HIV risk factor (n=1998)			
From high prevalence area	587 (87)	1126 (85)	
Injecting drug use	14 (2)	39 (3)	
Other*	70 (10)	162 (12)	χ^2, 2.79, p=0.248
Gestational age (n=1661)			
≥ 37 weeks	476 (82)	910 (84)	
< 37 weeks	101 (18)	174 (16)	χ^2, 0.58, p=0.448
Maternal age at delivery (years) (n=2089)			
< 25	105 (15)	275 (20)	
25-29	221 (31)	477 (34)	
30-34	227 (32)	403 (29)	
> 35	149 (21)	232 (17)	χ^2, 14.09, p=0.003
Antenatal antiretroviral therapy exposure (n=2075)			
None	23 (3)	81 (6)	
Monotherapy	156 (22)	290 (21)	
Double therapy	17 (2)	45 (3)	
3 or more drugs	501 (72)	962 (70)	χ^2, 7.86, p=0.049

Note: data as reported to the National Study of HIV in Pregnancy and Childhood by the end of August 2005. *Contact with infected blood, HIV infected partner, blood transfusion recipient

7.5 The health professional survey: clinic practice and involvement in the CHART study

7.5.1 Survey respondents

By the end of the data collection period, questionnaires had been returned by 40 out of the 46 health professionals contacted, a response rate of 87% (see Section 2.6 and Appendix 7). Of the six health professionals who failed to return the questionnaire, four

were from hospitals in London with a mean of 25 uninfected children born between January 2001 and April 2004 and reported to the NSHPC by April 2005; and two were from hospitals outside London (4 and 13 uninfected children reported).

The majority of the 40 respondents were paediatricians (20, 50%) or paediatric nurses (15, 38%). Other respondents were: three neonatologists, an HIV physician, and a paediatric secretary. Health professionals' views on the long-term follow-up of ART-exposed uninfected children (section C of the questionnaire) are presented in Chapter 8 along with those of parents and carers.

7.5.2 Clinic practice regarding uninfected children

The annual number of uninfected children seen in clinic varied considerably between the 40 hospitals (Table 7.6). Just under half the respondents reported that uninfected children were seen in a general paediatric (15, 38%) or a neonatal (3, 8%) clinic; and a small number (4, 10%) specified a paediatric infectious diseases or blood borne virus clinic. In the remaining hospitals, they were seen in a dedicated HIV clinic: either a paediatric (8, 20%) or a family (10, 25%) clinic. Whether uninfected children were seen in an HIV clinic was not related to clinic caseload.

Table 7.6 Approximate number of uninfected children born to HIV infected women seen per year in clinic as reported by survey respondents

Uninfected children (n)	Respondents (n)
≤10	10
11-30	18
31-50	7
>50	3
Not provided	2
Total	**40**

To assess the multidisciplinary nature of the clinic, respondents were asked if they had regular discussion of issues relating to uninfected children with colleagues in other departments within their hospital. Three quarters (30, 75%) did so with colleagues both in the antenatal or obstetrics department and in the GU medicine or adult infectious disease department; and a further nine with colleagues in one of these two disciplines. One respondent (an HIV physician) discussed issues with colleagues in the paediatrics department.

In terms of the routine clinic follow-up protocol for a child born to a woman diagnosed with HIV, there was little variation between hospitals as to when this was done. Of the 39 respondents who supplied information on this, all offered clinic appointments at least once when the child was between six and eight weeks of age; and again at the age of three (36 respondents) or four months (1 respondent) or both (2 respondents). All but one of the respondents reported that it was clinic policy to invite children who had negative virological tests early in life to come back to clinic for a confirmatory antibody test between the ages of 12 and 18 months. Additional appointments were offered in some clinics: at six months (8 respondents), nine months (1 respondent) and yearly from 18 months until five years of age (7 respondents).

7.5.3 Involvement in the CHART study

Of the 40 survey respondents, 35 had participated in the CHART study and therefore completed section B of the questionnaire (Appendix 7). Comments made by the respondents are in Appendix 8.

Seven respondents reported that their involvement in the CHART study had formally changed their clinic policy in terms of how uninfected children were followed up. In two

hospitals, children had previously been discharged around 18 months of age, but with the introduction of the study, follow-up was extended beyond this age. In three hospitals, involvement in the study helped formalise annual follow-up. Twelve respondents considered that their involvement in the CHART study had informally changed clinic practice. Ways in which this occurred were: more time spent with parents to discuss the study and to complete the forms, more discussion with parents about exposure to ART, changes to the times of clinics, additional clinics arranged, and the offer of clinic appointments to children who would previously not have been seen after 18 months of age.

About a third (10/34, 29%) of respondents involved health professionals outside their clinic to assist with contacting parents and carers and enrolling children in the CHART study. Mostly these were GU physicians or nurses, though GPs, community paediatricians and nurses were also involved.

The approximate amount of time additional to routine clinical care that the respondent estimated that they and other colleagues had devoted to contacting parents and carers and enrolling children varied (Table 7.7). As expected, respondents in hospitals with more children who fitted the inclusion criteria for the CHART study tended to devote more time to it. One respondent commented that the forms were easy to complete within normal consultation time, but another felt "uneasy" asking families back to clinic for a "few simple questions" so they also did an examination on the child (Appendix 8).

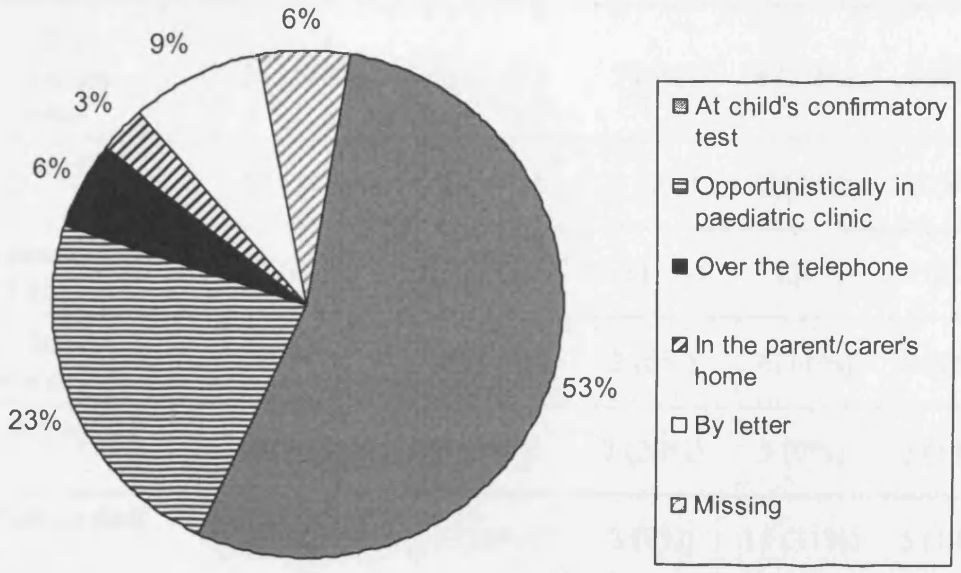
Table 7.7 Estimated time spent contacting parents/carers and enrolling children into the CHART study

Time	Respondents (n)
Less than 1 hour per month	9
1-2 hours per month	16
1 hour per week	5
More than 1 hour per week	2
Not provided	3
Total	**35**

Contacting parents and carers about the CHART study

Three quarters of respondents usually approached parents and carers about the CHART study in the paediatric clinic, either when the child was brought to clinic for their confirmatory antibody test or at another time (Figure 7.3).

Figure 7.3 How health professionals usually approached parents/carers about the CHART study (n=35)



Respondents were asked about situations which made contacting parents and carers about the CHART study difficult (Table 7.8). Clinic non-attendance and loss of contact were considered especially problematic, particularly as some families moved or were moved away or changed their telephone number (see Appendix 8). Some families were reluctant to be contacted by the clinic staff, particularly once the child was discharged. Specific reasons given for this included the father or partner not being aware of the mother's HIV status, and families not wanting to be reminded about HIV once their child was known to be uninfected. In addition, a number of respondents sometimes felt awkward when they tried to contact families who had already been discharged from the clinic. Other issues highlighted were lack of resources and large clinic caseload (Appendix 8).

Table 7.8 Frequency with which respondents thought certain situations made contacting parents/carers about the CHART study difficult (n=35)

Situation	Frequently n (%)	Sometimes n (%)	Hardly ever n (%)	Never n (%)	Missing n (%)
Regularly does not attend scheduled appointments	12 (34%)	13 (37%)	2 (6%)	4 (11%)	4 (11%)
Lost contact with family	12 (34%)	16 (46%)	3 (9%)	2 (6%)	2 (6%)
Family known to have left the UK	2 (6%)	13 (37%)	6 (17%)	7 (20%)	7 (20%)
Difficult family circumstances	3 (9%)	17 (49%)	2 (6%)	4 (11%)	9 (26%)
Child discharged from clinic	9 (26%)	11 (31%)	7 (20%)	3 (9%)	5 (14%)
Lack of clinic staff time	7 (20%)	9 (26%)	3 (9%)	11 (31%)	5 (14%)

Enrolment in the CHART study

Respondents were asked about why they thought parents and carers agreed to take part in the CHART study (Table 7.9). Over half of respondents indicated that wanting to keep in contact with health services was either frequently or sometimes important, slightly more so than concern over the safety of ART.

Table 7.9 Issues involved in parents/carers agreeing to take part in the CHART study: respondents' views (n=35)

Issue	Frequently n (%)	Sometimes n (%)	Hardly ever n (%)	Never n (%)	Missing n (%)
Concern over the safety of the antiretroviral therapy	9 (26%)	9 (26%)	5 (14%)	4 (11%)	8 (23%)
Wanting to keep in contact with health services	3 (9%)	16 (46%)	6 (17%)	3 (9%)	7 (20%)
Feeling uncomfortable about refusing	1 (3%)	8 (23%)	9 (26%)	6 (17%)	11 (31%)

Respondents were then asked how often they thought several different issues were involved in parents and carers declining to take part in the CHART study (Table 7.10). Nearly half of respondents thought concern about data confidentiality was frequently or sometimes involved. Other issues mentioned were: the parent not wanting to be reminded of their illness, and families not wanting to come to clinic appointments in nursery or school time.

Table 7.10 Issues involved in parents/carers declining to take part in the CHART study: respondents' views (n=35)

Issue	Frequently n (%)	Sometimes n (%)	Hardly ever n (%)	Never n (%)	Missing n (%)
Not feeling that it is important	2 (6%)	9 (26%)	4 (11%)	10 (29%)	10 (29%)
Not wanting to keep in contact with health services	4 (11%)	10 (29%)	6 (17%)	9 (26%)	6 (17%)
Difficult family circumstances	1 (3%)	12 (34%)	7 (20%)	6 (17%)	9 (26%)
Concern about data confidentiality	6 (17%)	10 (29%)	3 (9%)	8 (23%)	8 (23%)

7.6 Key points

- just over 2100 uninfected children reported to the NSHPC from nearly 170 hospitals in the UK were eligible for enrolment in the CHART study
- at the end of the study period, a third of eligible children had been enrolled, parents/carers of 5% had declined enrolment, a quarter were lost to follow-up or had left the UK, and a third were not enrolled because the health professional was unwilling to contact the family
- of the enrolled children 7% were subsequently reported as lost to follow-up, and the parents/carers of 2% declined further follow-up
- confidentiality was the most frequently given reason for the parent/carer declining enrolment
- the family having moved or changed contact details was the most frequently given reason for loss to follow-up

- the majority of eligible children were born to women from sub-Saharan Africa, and only 3% of children were born to women who had acquired HIV infection through injecting drug use
- 95% of eligible children had been exposed to antenatal ART, mostly combination therapy
- enrolled and non-enrolled children were similar in terms of demographic characteristics, but enrolled children were more likely to have been exposed to antenatal ART
- most health professional survey respondents were paediatricians or paediatric nurses
- the majority of respondents offered clinic appointments for uninfected children at 6-8 weeks, 3 and/or 4 months and 12-18 months of age; a fifth of respondents then offered appointments annually until 5 years of age
- a fifth of respondents reported that their involvement in the CHART study had formally changed clinic policy in terms of how uninfected children were followed up, and a third reported that it had informally changed clinic practice
- a third of respondents had involved health professionals outside their clinic to assist with study enrolment
- three quarters of respondents usually approached parents/carers about the study in the paediatric clinic
- clinic non-attendance and loss of contact were considered situations that often made contacting parents/carers about the study difficult
- over half of respondents thought keeping in contact with health services was either frequently or sometimes involved in parents/carers agreeing to take part in the study
- nearly half of respondents thought concern about data confidentiality was either frequently or sometimes involved in parents/carers declining to take part in the study

Chapter 8 Views of parents and carers on the long-term follow-up of uninfected children

"When you are pregnant you are worried about the virus passing to baby and not strongly about the effects of the drugs."

[Mother of one child (aged 3 months)]

"We don't know the outcome of these drugs so we shouldn't hesitate with investigations."

[Father of four children (aged 1, 4, 14 and 15 years)]

8.1 Introduction

Clinic-based follow-up of uninfected children may not always be appropriate for HIV-affected families. As was observed in the CHART study, some families declined and a large number of children were lost to follow-up before the health professional could approach the family about enrolment (see Chapter 7). Possible adverse effects associated with antiretroviral therapy (ART) exposure may not develop for many years, even into adulthood; therefore it is important that monitoring continues beyond the time when the family is in regular contact with HIV-related services. As there are strategies that could be used over the long term which involve the family and health professionals to a lesser extent than clinic-based follow-up, it is appropriate to obtain views of parents and carers to inform proposals for the future. In this chapter, results from a questionnaire survey with parents and carers of uninfected children are presented. Findings from the survey are compared with results from a related survey among health professionals (Section 8.6). Further details on the surveys are provided in Chapter 2.

8.2 Survey respondents

There were 140 respondents in total; 137 from the 14 clinics involved in the survey and three from Positively Women and Positive Nation. Seventy six respondents were recruited from the six researcher clinics. The clinic attendance rates on the occasions when the researcher was present were available for four of the five paediatric clinics (Table 8.1). The overall attendance rate for each of the four clinics varied from 56% to 87%. Not all parents and carers who attended the clinic with their child met the inclusion criteria as some only cared for an infected child and others for a young infant of indeterminate status. Furthermore, due to the set up of individual clinics, some of those who met the inclusion criteria left the clinic before they could be approached. The response rate for those invited to participate in the six researcher clinics was 85% (76/89)

(Table 8.1). The majority of respondents completed the questionnaire in the clinic (74/76, 97%). Two parents took the questionnaire home to complete, and both returned it by post.

The remaining 61 respondents were from eight non-researcher clinics (Table 8.2). The response rate for parents and carers invited in clinic to participate was 93% (43/46); with a much lower response rate for those who were sent the survey material (18/55, 33%).

8.3 Respondents and their children

Just over half of the 140 respondents (74, 53%) cared for one child born to an HIV infected woman; a further 39 (28%) cared for two, 18 (13%) for three, and nine (6%) cared for four or more children. The majority of respondents (127/139, 91%) were mothers of the children in their care, 11 respondents were fathers and one respondent was an aunt.

A total of 135 respondents reported their own country of birth. Of the maternal respondents, 11 (11/123, 9%) were born in the UK, 105 (105/123, 85%) in sub-Saharan Africa (see Table 8.3) and the remainder in Jamaica (2), New Zealand (1), Iraq (1), Russia (1) and Portugal (1). Of the 12 non-maternal respondents, four were born in the UK and the rest in sub-Saharan Africa (Ghana, Angola, Republic of the Congo, Rwanda, Uganda and Zimbabwe).

Most respondents (134/138, 97%) expected that the children in their care would continue to live in the UK; and of the four who did not, three thought they would leave the UK within five years and one did not know when they would leave.

Table 8.1 Attendance rates and response rates in researcher clinics involved in the parent and carer survey

Hospital* (type of clinic)	Data collection period	Number of clinics visited by researcher	HIV-affected children booked for clinics that the researcher visited			Parents/carers who fitted inclusion criteria#			
			Booked (n)	Attended (n)	Attendance rate (%)	Total (n)	Invited to participate (n)	Completed questionnaire (n)	Response rate (%)
1 (PAED)	October 2004 - April 2005	7	34	19	56	16	15	12	80
2 (PAED)	November 2004 - June 2005	11	N/A	N/A	N/A	N/A	29	26	90
3 (PAED)	December 2004 - February 2005	4	44	28	64	16	13	10	77
4 (PAED)	February 2005 - June 2005	4	22	15	68	16	12	9	75
5 (PAED)	February 2005 - March 2005	2	23	20	87	9	7	7	100
5 (GU)	May 2005 - June 2005	5	Not applicable	Not applicable	Not applicable	N/A	13	12	92
Total	**October 2004 - June 2005**	**33**	-	-	-	-	**89**	**76**	**85**

*The hospitals involved in the parent and carer survey are listed in Appendix 9
PAED, paediatric clinic; GU, genitourinary clinic; N/A, information not available
#Parent/carer who cared for at least one uninfected child born in the UK to an HIV infected woman who took antiretroviral therapy during pregnancy

Table 8.2 Response rates in non-researcher clinics involved in the parent and carer survey

Hospital* (type of clinic)	Data collection period	Parents/carers who fitted inclusion criteria# and were invited to participate in clinic			Parents/carers who fitted inclusion criteria# and were sent survey information		
		Invited to participate (n)	Completed questionnaire (n)	Response rate (%)	Sent survey information (n)	Returned questionnaire (n)	Response rate (%)
3 (GU)	June 2005 - August 2005	17	17	100	-	-	-
6 (PAED)	December 2004 - July 2005	9	9	100	-	-	-
7 (PAED)	January 2005 - May 2005	4	2	50	-	-	-
8 (PAED)	January 2005 - March 2005	2	1	50	4	2	50
9 (PAED)	February 2005 - April 2005	-	-	-	10	3	30
10 (PAED)	March 2005 - July 2005	6	6	100	5	3	60
11 (PAED)	December 2004	-	-	-	8	1	10
12 (PAED)	March 2005 - April 2005	8	8	100	28	9	32
Total	**December 2004 - August 2005**	**46**	**43**	**93**	**55**	**18**	**33**

*The hospitals involved in the parent and carer survey are listed in Appendix 9
PAED, paediatric clinic; GU, genitourinary clinic
#Parent/carer who cared for at least one uninfected child born in the UK to an HIV infected woman who took antiretroviral therapy during pregnancy

Table 8.3 Country of birth of maternal respondents born in sub-Saharan Africa (n=105)

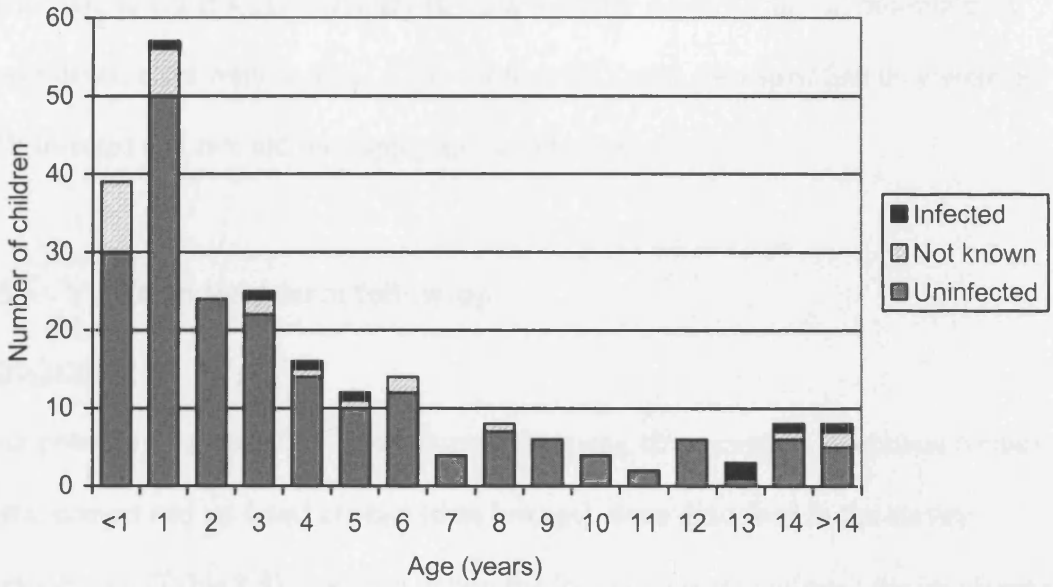
Country	n	%
Cameroon	3	3
Democratic Republic of the Congo (Zaire)	4	4
Ghana	11	10
Ivory Coast	3	3
Kenya	6	6
Nigeria	9	9
Rwanda	3	3
Sierra Leone	3	3
South Africa	5	5
Uganda	21	20
Zambia	7	7
Zimbabwe	19	18
Other*	11	10

*Angola (1), Burundi (2), Ethiopia (2), Gambia (1), Malawi (2), Republic of the Congo (1), Somalia (2)

Generally there was only one respondent per family, but five of the fathers and the aunt who participated came from the same family unit as a maternal respondent. There were a total of 239 children cared for by the respondents and the median age of the children was two years (range 4 weeks to 17 years) (Figure 8.1).

Every family included at least one uninfected child because of the inclusion criteria, but in fact most of the 239 children were uninfected (206/239, 86%); eight were infected and the infection status of 25 children was not known (indeterminate status or not tested) (Figure 8.1). Results of blood tests were not requested on the questionnaire. A total of 46 children were born outside the UK (46/233, 20%) and all of these had at least one younger sibling who was born in the UK. Of the eight infected children, six were born outside the UK.

Figure 8.1 Age and infection status of the children cared for by the respondents



8.4 Contact with health services

As clinic-based follow-up is dependent on the relationship between families and service-providers, respondents were asked about their contact with and disclosure to health professionals. For the 132 respondents with no infected children, those whose youngest child was less than two years of age were more likely to still visit the paediatric or family clinic for their children's care (84/88, 95%) than those whose youngest child was aged two years or older (20/42, 48%) (χ^2, 40.66, $p<0.001$).

Almost all respondents took their children to a general practitioner (GP) in addition to HIV-related follow-up in clinic (135/139, 97%). Disclosure of HIV status to the GP was relatively common: 81% (109/135) of respondents reported that their GP knew about HIV in the family. A further 18 respondents had not told their GP, and seven respondents did not know if their GP knew. Whether disclosure to the GP had occurred was not associated with the age of the youngest child cared for.

All 124 maternal respondents who reported where they received their own HIV care from, went to either a genitourinary (GU) or a family clinic. Of the 12 non-maternal respondents, eight went to a GU clinic for their HIV care, two specified they were not HIV infected and two did not supply any information.

8.5 Views on long-term follow-up

Introduction

Four possible long-term follow-up options involving clinic contact, telephone contact, postal contact and no direct contact (data linkage), were described in the survey questionnaire (Table 8.4). For each option the following were outlined: the involvement of the parent/carer, clinic staff and researchers; who would need to know the parent/carer's contact details; who would receive information on the child's health. Through the information sheet (Appendix 10), researchers at the Institute of Child Health were introduced, so that words such as "us" and "we" could be used in the description of the options.

Options were chosen to provide a range of intensity of contact that the parent or carer would have with the clinic and researchers. As the CHART study protocol represented an intensive type of contact and as survey respondents would not necessarily have been approached about enrolment in the study, two of the options (clinic and telephone) were based on the CHART study protocol (see Section 2.3 and Chapter 7). As lack of clinic resources was a factor in enrolment and sustainability of the CHART study, direct postal contact between the family and researchers was proposed in one option. Linkage between health records and routinely available health data does not involve direct contact, and was the least intensive form of contact outlined in the questionnaire. This option related to a general data linkage study and not particularly the Office for National

Statistics flagging study (Chapter 6). Respondents were asked a series of questions on the four options (see Appendix 11).

Table 8.4 The four follow-up options presented in the survey questionnaire

OPTION A (CLINIC CONTACT) • You and/or your child would be asked to come to the family or paediatric clinic once a year. • Clinic staff would ask you general questions about your child's health. • The answers would be put on a form and sent to us. Neither your name nor your child's name would be on the form. • You would need to inform the clinic of any change in your contact details.
OPTION B (TELEPHONE CONTACT) • Clinic staff would telephone you once a year and would ask you general questions about your child's health. • The answers would be put on a form and sent to us. Neither your name nor your child's name would be on the form. • You would not need to attend the clinic to take part, but you would need to inform the clinic of any change in your telephone number.
OPTION C (POSTAL CONTACT) • The clinic staff would give us your contact details when your child was discharged. We would keep these in strict confidence. • We would send you a short form about your child's health once a year, for you to complete and send back to us. • There would be no reference to HIV on anything you were sent. • You would need to inform us of any change in your address.
OPTION D (NO DIRECT CONTACT) • We would not need to have any regular direct contact with you or your child and we would not know your or your child's name or address. • Every child in the UK is given an NHS number at birth. The clinic would give us your child's NHS number which we could relate to routinely available health information. • You would not have to keep in contact with the clinic after your child was discharged.

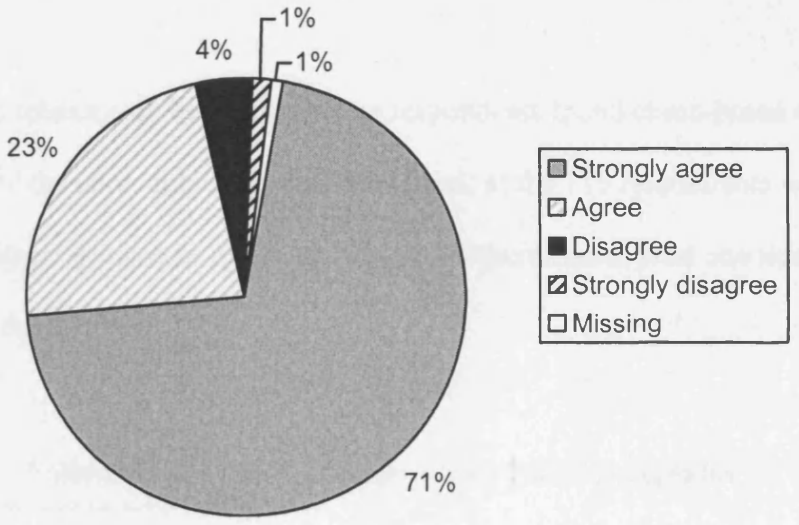
Importance of follow-up

Nearly all of the respondents (131/139, 94%) agreed with the statement: "it is important to follow up uninfected children to see if there are any side effects from anti-HIV drugs" (Figure 8.2). Some of them added further comments supporting this and their reasons

included: the uncertainty of whether side effects would occur in the future, reassurance for the parent, and a way of children helping others in the same situation. Two respondents thought follow-up was important, but only if there was a health problem identified, and two more respondents suggested specific problems that may affect a child exposed to ART: weight loss and fertility problems (see Appendix 12).

Figure 8.2 Importance of follow-up: respondents' agreement (n=140)

"It is important to follow up uninfected children to see if there are any side effects from anti-HIV drugs"



Acceptability

Respondents were asked which option or options presented in the questionnaire (Table 8.4) they thought acceptable. All respondents except one considered at least one of the options acceptable: 60% (84/140) thought one acceptable, 19% (26/140) two, 11% (15/140) three and 10% (14/140) all of them. Overall, annual clinic-based contact was considered to be the most appropriate with 61% (86/140) finding it acceptable to come to the clinic (option A) and 48% (67/140) to be telephoned by the clinic (option B). Fewer respondents found postal contact with the researchers (option C) (51/140, 36%) or the no

direct contact option (option D) (33/140, 24%) acceptable (Table 8.5). Whether respondents reported option A acceptable was not associated with family characteristics: age of the youngest child (less than two years versus two years or older) (χ^2, 1.12, p=0.289), whether the respondent was born in the UK (χ^2, 2.37, p=0.123) or the number of children they cared for (one versus two or more) (χ^2, 1.52, p=0.218). The same was also observed for option C and option D. Respondents who had two or more children were more likely to find option B acceptable (34/66, 52%) than those with one child (21/74, 28%) (χ^2, 7.83, p=0.005), though there was no association with other family characteristics.

There was no relationship between whether respondents found clinic-based contact acceptable and the clinic they were recruited from: of the 115 respondents who considered either option A or option B acceptable, there was at least one from each of the 14 clinics in the survey.

Table 8.5 Follow-up options that respondents found acceptable

Option(s)	n (%)
All 4 options	14 (10)
A + B + C	11 (8)
A + B + D	1 (1)
A + C + D	3 (2)
B + C + D	0 (0)
A + B	12 (9)
A + C	6 (4)
A + D	1 (1)
B + C	3 (2)
B + D	2 (1)
C + D	2 (1)
A only	38 (27)
B only	24 (17)
C only	12 (9)
D only	10 (7)
None of them	1 (1)
Total	**140**

Notes: A=clinic contact, B=telephone contact, C=postal contact, D=no direct contact

As previously mentioned, the four options varied in terms of the intensity of contact that the family would have with the clinic and researchers. Each option was given a score to reflect this: A=4, B=3, C=2 and D=1. Based on the combination of options that the respondent found acceptable, an intensity score was calculated. There was no significant difference in the mean intensity score between: respondents whose youngest child was aged less than two years and those whose youngest child was two years or older (4.88 versus 4.86, t=0.03, p=0.974); respondents born in the UK and those born abroad (5.66 versus 4.83, t=1.12, p=0.263); respondents who cared for one child and those who cared for two or more (4.68 versus 5.05, t=-0.77, p=0.443).

Issues surrounding disclosure and confidentiality were raised by some respondents (see Appendix 12). Some were concerned that involvement in follow-up could mean that their HIV status would be disclosed to the child when either they had already decided not to disclose to their family, or had yet to decide whether to disclose. This was mentioned particularly in relation to clinic-based contact. Some respondents stated they did not want their child to know about their HIV status because it would be difficult for the child to "accept or understand", they did not want to "harm or scare them" or they wanted their child to be "normal". One respondent thought GPs should be aware of any follow-up as she wanted to keep "family health care as 'normal' as possible", while another was "happy to help with research if totally anonymous".

A quarter of respondents strongly objected to at least one option (31/136, 23%), in particular postal contact (15 respondents). Reasons for objecting were given by 25 of the respondents (Table 8.6). These were generally because they specifically wanted another type of contact for the child, they envisaged logistical problems or they were concerned about confidentiality with their child, family or neighbours.

- *"Once your child has been cleared the last thing you want is to come to hospital for these visits. Children grow up and will start asking questions."*
- *"Don't want to be written to because I live with my sister and someone could open the letter."*

Table 8.6 Follow-up options that respondents strongly objected to and reasons given (n=31)

Options strongly objected to	Number of respondents (n)	Reason (n)
A only	2	Difficult to explain reason to child (2)
B only	4	Someone else could hear conversation (3) Prefer eye contact (1)
C only	11	Someone else could read information (6) Do not want details to leave clinic (2) Cannot read (1) No reason given (2)
D only	9	Want to give consent (2) Want to be seen in clinic (2) Do not want child "labelled" (1) No reason given (4)
A + B	1	Do not like contact with medical professionals (1)
C + D	1	Do not want child on a "register" (1)
B + C	1	Want to be seen in clinic (1)
B + C + D	1	Want to be seen in clinic (1)
A + B + C	1	Work abroad (1)

Notes: A=clinic contact, B=telephone contact, C=postal contact, D=no direct contact

Parental permission

Respondents were asked if they thought parental permission would be needed before a child was included in option D (no direct contact). Of the 130 respondents who answered this question, 70% (n=91) indicated that it would be needed. In terms of when parents and carers should be asked for permission before a child was included in any type of follow-up, 40% of respondents (55/136) thought this should occur during pregnancy,

10% (14/136) at birth and 38% (51/136) when the child was known to be uninfected. Ten respondents wanted the issue to be raised at more than one stage (see Appendix 12).

Contacting parents and carers

Respondents were asked whether, if a health problem associated with exposure to a particular antiretroviral drug was identified in children, parents and carers should be told about the risk. The majority of respondents thought they should be told regardless of whether there was any treatment available for the health problem (118/140, 84%) and a smaller number (n=19) only if there was a treatment available.

- *"If there is something ahead you should contact the Mum (if I'm still alive)."*

Three of the respondents did not think the parents and carers should be told of a risk.

- *"If the children aren't ill, then they* [the parents] *shouldn't be told."*
- *"You would know if your child was ill but I wouldn't want to know if others were ill."*

Of the 10 respondents who only found option D acceptable, nine of them still indicated that parents and carers should be told of a risk to the child's health.

When asked how parents and carers should be contacted about any such risk, a letter from the paediatric or family clinic was the most popular option (50/133, 38%) with 12 also specifying that they should be offered a clinic appointment. About a third of respondents (43/133) stated a telephone call from the clinic was the most appropriate, and a small number (n=9) both a telephone call and a letter from the clinic. A letter from researchers outside the clinic was thought by nearly a fifth (23/133) to be the best way of contacting the family. In terms of methods of contact, there were some apparent contradictions within individuals. Of the 23 respondents who thought a letter from the researchers to be the most appropriate channel for communication of a risk, only eight

found follow-up option C acceptable; and of the 44 respondents who indicated that a telephone call from the clinic would be suitable, only 26 thought option B was acceptable.

Contact via parents and carers or young person?

As possible health problems associated with exposure to ART may not become apparent for many years, it was proposed in the questionnaire that at some stage it might be more appropriate for the clinic or researchers to have direct contact (options A-C) with the young person themselves rather than the parent or carer. Respondents were asked what they thought about this.

Eighteen out of the 105 respondents who answered this question (18/105, 17%) stated that the young person should be contacted directly by the clinic or researchers, and six of the 18 specified this would be appropriate when the child was: an adult (2), a teenager (1), "more mature" (1), 16 years old (1) or 18 years old (1). Five of the 18 respondents thought direct contact could only occur in the following situations: if the child knew about the mother's HIV status (3), if the parent was dead (1), or if the parent had given permission (1) (see Appendix 12).

Most respondents (77/105, 73%) thought it should be up to the parent or carer to tell the clinic or researchers if and when the young person could be contacted. Some respondents gave reasons for this: they did not want anyone else contacting their child at all or without their permission, it was more appropriate if the parent discussed the subject with the child before anyone contacted them, they would not want to upset the child, the child might not know about their parent's HIV status or the parent might not plan to tell them,

and involving the parent would assist in the disclosure of their HIV status to the child (see Appendix 12).

Three respondents did not know how contact at a later stage should be done, two thought this would be the child's choice, four did not want any direct contact and one did not want any direct contact after the child was five years old (see Appendix 12).

8.6 Views on long-term follow-up: health professional survey and parent and carer survey

Four of the questions on the importance and acceptability of long-term follow-up from the parent and carer survey questionnaire were included on the health professional survey questionnaire to compare responses (see Section 2.6 and Appendix 7). The description of the four follow-up options was adapted as appropriate. Details on the 40 health professional survey respondents are given in Chapter 7.

All of the health professionals agreed that "it is important to follow up uninfected children to see if there are any side effects from anti-HIV drugs", similar to the 94% of parents and carers who agreed.

Half of the health professionals (22/40, 55%) indicated that parents should initially be asked during pregnancy for permission to follow up the child. Four (10%) thought permission should be asked for at birth and 14 respondents (35%) thought parental permission should be asked for when the child was known to be uninfected (see Appendix 8). The stage at which health professionals reported that parental permission should be asked was similar to what was observed with parents and carers (40%, 10% and 38% for the three stages respectively).

All health professionals thought at least one of the options acceptable. They were generally more likely to find three (11/40, 28%) or four (6/40, 15%) options acceptable than the parents and carers (11% and 10% respectively). Option A was the option that most health professionals found acceptable (28/40, 70%) and was of a similar proportion to that of the parents and carers (61%) (χ^2, 0.984, p=0.321). However, option D was reported to be acceptable by a larger proportion of health professionals (21/40, 53%) than of parents and carers (33/140, 24%) (χ^2, 12.398, p<0.001) and similar was observed for option C (χ^2, 4.451, p=0.035). Health professionals from five of the 12 hospitals where the parent and carer survey was carried out found all of the options acceptable; and each option was found acceptable by at least one parent or carer in each hospital. In six of the seven remaining hospitals, parents and carers found options acceptable when the health professional did not (option A in 4 hospitals, B in 2, C in 3 and D in 1). Furthermore, in two hospitals, the health professional found options acceptable when none of the parents and carers did (option A and D in one hospital and C and D in the other).

There were some issues relating to options A and B that were highlighted by the health professionals: difficulties in dedicating clinic time and resources and the mobility of the families involved. Problems raised in terms of option C were perceived low response rates and difficulties in families receiving the documents, again due to their mobility and because many live in shared accommodation (see Appendix 8).

Nearly half of the health professionals strongly objected to at least one of the options in the questionnaire (15/34, 44%), a higher proportion than the parents and carers (31/136, 23%) (χ^2, 6.266, p=0.012) (Table 8.7). Eight health professionals cited lack of clinic resources as a reason for objecting to option A or option B, however this was not associated with clinic caseload.

- *"Unnecessary contact with clinic creates huge anxieties in families. Also difficult to justify in the present climate of limited resources."*
- *"Quite a few of our families live in accommodation where there are lots of people and may not want to discuss things on the phone."*

Table 8.7 Follow-up options that health professional survey respondents strongly objected to and reasons given (n=15)

Options strongly objected to	Number of respondents (n)	Reason(s) (n)
A only	5	Lack of clinic time/resources (2) Lack of clinic time/resources & parental confidentiality concerns (3)
B only	5	Time consuming & need interpreters (1) Time consuming & intrusive (1) Intrusive (1) Parental confidentiality concerns (1) Families change telephone numbers often (1)
C only	2	Problematic to families(1) Parental confidentiality concerns (1)
D only	2	Not enough contact (2)
A + B	1	Lack of resources (1)

Notes: A=clinic contact, B=telephone contact, C=postal contact, D=no direct contact

8.7 Key points

- most parent and carer survey respondents were born in sub-Saharan Africa and were mothers of the children in their care
- median age of the children in the care of the respondents was two years
- of respondents with no infected children, those whose youngest child was aged less than two years were more likely to still visit the paediatric or family clinic than those whose youngest child was two years or older
- among respondents who took their children to a GP, most had told the GP about HIV in the family

- almost all parents and carers thought it was important to follow up uninfected children to see if there were side effects from ART
- annual clinic-based contact was thought the most acceptable type of follow-up, though a third of respondents found postal contact with researchers acceptable and a quarter found data linkage acceptable
- whether respondents found a particular type of follow-up acceptable was not generally associated with family characteristics
- a quarter of parents and carers strongly objected to at least one type of follow-up, mostly postal follow-up
- concerns regarding follow-up usually centred around disclosure, confidentiality and contact with health professionals
- two thirds of parents and carers indicated that parental permission would be needed before a child was included in data linkage
- the majority of respondents thought parents and carers should be told of a health problem associated with exposure to a particular antiretroviral drug
- over three quarters of respondents thought that direct contact should be through the parent or carer rather than with the young person; concerns over disclosure and appropriateness were cited
- all health professional survey respondents thought it was important to follow up uninfected children to see if there were side effects from ART
- health professionals generally found more types of follow-up acceptable than parents and carers
- about half of health professionals thought data linkage acceptable, a larger proportion than that of parents and carers
- nearly half of health professionals strongly objected to at least one type of follow-up, a larger proportion than that of parents and carers

- concerns relating to follow-up raised by health professionals were clinic resources, confidentiality and mobility of HIV-affected families

Chapter 9 Discussion

9.1 Background

The use of highly active antiretroviral therapy (HAART) has considerably altered the natural history of HIV infection in Europe. Mortality rates among HIV infected individuals have decreased and HIV has become a manageable chronic disease (Mocroft *et al.* 2003, CASCADE Collaboration 2000, European Centre for the Epidemiological Monitoring of AIDS 2005).

HIV infected women who are aware of their diagnosis may choose to become pregnant because they are in good health and are able to access appropriate interventions to prevent mother-to-child transmission (MTCT) (Fiore 2005, Newell *et al.* 2002). In addition, the introduction of antenatal HIV testing programmes has led to a considerable increase in detection rates among previously undiagnosed HIV infected women (The UK Collaborative Group for HIV and STI Surveillance 2005). With the use of interventions, MTCT rates of less than 2% can be achieved (Mandelbrot *et al.* 2001, European Collaborative Study 2005c). The increasing number of pregnancies among diagnosed HIV infected women, combined with the widespread administration of antiretroviral therapy (ART) in pregnancy and in the neonatal period, has resulted in an increasing number of uninfected children who were exposed to ART (European Collaborative Study 2005c, Tookey 2005b).

In resource-rich settings, national guidelines have been established which recommend the use of prophylactic ART to prevent MTCT; many HIV infected pregnant women also require treatment for their own HIV infection (Public Health Service Task Force 2005a, Hawkins *et al.* 2005, Newell *et al.* 2002). In Europe, estimates of MTCT rates in the

absence of interventions range from about 15% to 30% (The Working Group on Mother-to-Child Transmission of HIV 1995, Ratcliffe *et al.* 1998); the different estimates are probably at least partly related to the background rates of breastfeeding and caesarean section delivery in different European settings. Therefore in order to protect the minority of HIV-exposed children who would be infected if no action were taken, all HIV infected pregnant women are advised to take ART; this means that virtually all of their children are exposed to the potential unwanted side effects of such treatment, alongside the undoubtedly beneficial effect of avoiding HIV infection.

As there are concerns about possible long-term effects of exposure to antiretroviral drugs, it is important to identify practical and effective means of monitoring these children (Mofenson and Munderi 2002). Long-term cohort studies, which could potentially identify associations between ART exposure and adverse outcomes, only include a fraction of the actual number of uninfected children exposed to ART. Active surveillance is more comprehensive in terms of the population covered, though the amount of information collected at an individual level is limited.

9.2 HIV-affected families in Europe

In the European Collaborative Study (ECS), there has been an increase in the proportion of uninfected children born to black women from sub-Saharan Africa who acquired their HIV infection heterosexually, and a decrease in those born to white women with a history of intravenous drug use. In the mid 1980s, 5% of uninfected children in the ECS paediatric centres were born to black women and 93% were born to white women. However by the end of the study period, the proportion of children born to black women had increased to 46% and the proportion born to white women had decreased to 47% (Chapter 3). Similarly, in the early 1990s about two thirds of children reported to the

National Study of HIV in Pregnancy and Childhood (NSHPC) were born to women from sub-Saharan Africa, but this rose to about 80% in 2000-2004. National data collated by the European HIV/AIDS surveillance programmes show a similar picture (European Centre for the Epidemiological Monitoring of AIDS 2005). In the UK, three quarters of heterosexually acquired HIV infections diagnosed in 2004 were probably acquired in Africa (The UK Collaborative Group for HIV and STI Surveillance 2005).

Proxies for the early social environment of uninfected infants in the ECS were derived from maternal information collected during pregnancy (Chapter 3). This meant that only broad social circumstances were considered. No measures of maternal socio-economic status such as income, employment or housing were available. This was a limitation as HIV-affected families may be financially disadvantaged due to factors such as drug use or immigration problems, which could in turn affect access to services (Schrooten *et al.* 2002, Dray-Spira and Lert 2003).

Most of the approximately 1700 uninfected infants enrolled in the ECS paediatric centres were looked after by one or both of their parents. Over the study period, there was a decrease in the proportion of children requiring alternative (non-parental) social care in the first year of life. This was probably due to the reduction in the number of drug-using women whose children were at an increased risk of placement in alternative care, which has also been observed elsewhere (Blanche *et al.* 1996, Schable *et al.* 1995). Furthermore, the improved health and quality of life of HIV infected individuals as a result of HAART has meant that parents are better able to care for their child (Mocroft *et al.* 2003). Parental care as the main source of social care of children born to HIV infected women was also observed in a UK setting: almost all of the 140 respondents in the parent and carer survey were parents of the children in their care (Chapter 8).

The stigma associated with HIV infection has been recognised since the beginning of the epidemic. Women can be particularly affected by HIV-related stigma in terms of being labelled as promiscuous, a drug-user or a prostitute (Bunting 1996). Fear of discrimination or isolation is likely to influence decisions about disclosure of HIV status to family and friends, as well as to health professionals (Anderson and Doyal 2004). There are also cultural differences in terms of how HIV is perceived (Erwin *et al.* 2002). Concerns over immigration status may act as a barrier to accessing both HIV and general health care (Erwin and Peters 1999, Pollard and Savulescu 2004). HIV infected African women living in Europe are less likely to disclose their HIV status to family and friends than women originating from Europe (Bungener *et al.* 2000), which could limit their access to support with caring for their child. Active drug users may also have poor access to health services because of psychosocial factors (Mok *et al.* 1996).

Medical confidentiality is fundamental in health service provision, though the level to which individual patients want it is likely to vary (Jenkins *et al.* 2005). In a large descriptive study of views on medical privacy among patients with one or other of six chronic conditions, individuals with HIV were the least likely to report that others knew about their condition (Kass *et al.* 2004). Concern over confidentiality was the most frequently cited reason for parents declining enrolment in the CHART study (Chapter 7). Respondents in the parent and carer survey also mentioned their anxieties about confidentiality and the risk of inadvertent disclosure, as issues which made long-term contact and follow-up problematic for them (Chapter 8). The following statements were representative of the opinions expressed.

"Am happy to help with research if totally anonymous." [Mother of one child (aged 1 year)]

"I feel that keep the child under checks would bring some conflict. In my opinion I have chosen not to disclose my HIV status to my family." [Mother of one child (aged 3 years)]

Although most respondents to the parent and carer survey reported that they had disclosed their HIV status to the family general practitioner (GP), this is not always the case with HIV-affected families (Anderson and Doyal 2004). Anecdotal reports from the CHART study suggested that the family GP and health visitor were not always aware of the mother's HIV infection and therefore could not be contacted regarding enrolment of the child in the study (Chapter 7). Even if disclosure to the GP has taken place, HIV-affected families may still prefer to receive their care from the paediatric HIV clinic which offers familiarity and security (Boulton *et al.* 1999). The level to which individuals involve their GP is likely to vary, as suggested by one mother in the parent and carer survey:

"I think that GPs must be aware of any follow-up programme. I know some families with HIV are not always comfortable with this- but personally I find it crucial to keep our family health care as 'normal' as possible- less explaining, and I think less stigmatised." [Mother of one child (aged 6 years)]

The majority of respondents to the health professional survey reported offering clinic appointments at the standard ages recommended for testing children born to HIV infected women, as outlined in the British HIV Association pregnancy guidelines (Hawkins *et al.* 2005). However, non-attendance both in paediatric and genitourinary (GU) clinics was a particular barrier to enrolling children in the CHART study; and where a reason had been provided for loss to follow-up, clinic non-attendance was reported for about a third of children. Conversely, over half of respondents to the health professional survey thought many parents agreed to take part in the CHART study because they were keen to keep in contact with familiar health services (Chapter 7). This dichotomy is summed up by a paediatrician in the health professional survey:

"Two distinct groups of patients exist: 1- who would like engaging medical contact with non specific concerns. 2- who would want to cut off with us as soon as possible."
[Paediatrician]

Increasingly, hospitals are adopting a "family clinic" structure to care for HIV-affected families, where medical and psychosocial care for adults and their children (infected or uninfected) is integrated (Sharland *et al.* 2003). In a survey of service-providers from 15 paediatric HIV centres in Europe, some of which were ECS centres, most reported the coordination of adult and paediatric clinic teams within their hospital (Thorne *et al.* 1999). In the health professional survey, all respondents reported regular discussion of issues relating to uninfected children with colleagues in the obstetric and/or GU departments within their hospital and a quarter reported that uninfected children were seen in a family clinic (Chapter 7).

Early in the epidemic, HIV-affected families in the UK were largely based in London. However, they now increasingly live outside London, due in part to the epidemic becoming more generalised in the heterosexual population but mainly because of a national programme for the dispersal of asylum seekers (National AIDS Trust 2006, Creighton *et al.* 2004). This has had a significant impact on the workload of GU clinics outside London in recent years (Rajamanoharan *et al.* 2004). The prevalence of HIV infection (diagnosed and undiagnosed) among women giving birth in England outside London, has increased since 2000 (see Figure 1.5). Some regions have been particularly affected, for example in the North West of England prevalence doubled from 0.046% in 2003 to 0.089% in 2004 (The UK Collaborative Group for HIV and STI Surveillance 2005). Reports of pregnancies in diagnosed HIV infected women reflect these trends in overall prevalence, with the proportion of pregnancies reported from regions outside

London rising from 20% in 2000/1 to 47% in 2004/5 (Tookey 2005a). Furthermore, children eligible for the CHART study were reported from 168 hospitals across the UK.

HIV-affected families in the UK are generally a mobile population. They frequently move or are dispersed, sometimes at short notice (National AIDS Trust 2006). There is also considerable movement between the UK and other countries, either for temporary visits or for permanent moves. In the health professional survey, loss of contact with the family was reported as a major limiting factor to enrolling children in the CHART study:

"Difficulties with keeping in touch with families, often move frequently." [Paediatric nurse]

"...the difficulty for us health professionals was trying to contact some of the carers/parents, due to high mobility of our clients." [Paediatric nurse]

Although uninfected children born to HIV infected women in Europe may come from families that share broad characteristics, they will have individual needs, and health and social services should cater for this (Thorne *et al.* 1999).

9.3 Antiretroviral therapy exposure and the health of uninfected children

The proportion of uninfected children in the ECS who were exposed to ART *in utero* and/or in the neonatal period increased from 23% in 1994 to 100% in 2000 (Chapter 4). This was a reflection of the increased use of prophylactic ART across Europe after the results of the Pediatric AIDS Clinical Trial Group (PACTG) 076 trial were published (Connor *et al.* 1994). Furthermore, *in utero* exposure to combination therapy, predominantly HAART, increased from the mid 1990s. These trends have been observed in observational studies elsewhere in Europe (Bellon Cano *et al.* 2004, Barret *et al.* 2003) and in the USA (Cooper *et al.* 2002). In the UK, three quarters of children eligible for the

CHART study (born since 1996) were exposed to combination therapy *in utero* (Chapter 7). HAART is now the standard treatment for HIV infected individuals, and it is recommended that pregnancy should not preclude the use of optimal therapeutic regimens (Public Health Service Task Force 2005a).

Congenital abnormalities

In the ECS there was no association observed between antenatal ART use and the presence or pattern of congenital abnormalities (Chapter 4). This is consistent with findings from studies which only addressed zidovudine (ZDV) exposure (Sperling *et al.* 1998, Lipshultz *et al.* 2000), as well as more recent analyses in which infants were exposed to HAART (European Collaborative Study 2005a, Townsend *et al.* 2006, Watts *et al.* 2004). Although these studies provide reassurance, ongoing monitoring of congenital abnormalities in ART-exposed children is required, particularly in view of the increasing number of antiretroviral drugs that are initiated before conception and in the first trimester of pregnancy (Tookey 2005b, European Collaborative Study 2005c).

The purpose of the Antiretroviral Pregnancy Registry (APR), a large-scale passive reporting system, is to detect any major teratogenic effects of antiretroviral drugs administered to pregnant women. By 2005, the APR had a sufficient number of first trimester exposures to detect a two-fold increase in risk of birth defects for nine antiretroviral drugs. No increases were detected for eight of them, though a high frequency of birth defects after first trimester exposure to didanosine (ddI) was noted (6.4%) (Antiretroviral Pregnancy Registry Steering Committee 2005).

Adverse health events

The ECS finding that in the short-term uninfected children exposed to ART were no more likely to suffer from a serious adverse health event, including neurological or cardiac diseases, is encouraging. Furthermore, there was no evidence of excess mortality associated with exposure to ART (Chapter 4). This is in line with evidence from other studies (Chotpitayasunondh *et al.* 2001, Sperling *et al.* 1998). The investigation here did not involve specific tests for mitochondrial abnormalities, and thus findings from the French Perinatal Cohort Study could not be confirmed or rejected (Blanche *et al.* 1999). In contrast to a report from the French group, there was no observed association between ART exposure and febrile seizures in the first 18 months of life (Landreau-Mascaro *et al.* 2002).

Prematurity and growth

The previously reported association between antenatal ART exposure and prematurity (European Collaborative Study and the Swiss Mother + Child HIV Cohort Study 2000) persisted in uninfected infants, with the risk being especially pronounced when protease inhibitors were part of the regimen (Chapter 4). The relationship between the use of illicit drugs in pregnancy and an increased risk of prematurity has long been established (Mauri *et al.* 1995), and this was also observed here, independent of ART exposure.

Although in multivariable regression models, children exposed to combination therapy were significantly smaller in terms of weight, height and head circumference than those who were not exposed or who were only exposed to monotherapy, this effect was small (adjusted coefficients -0.10, -0.12, -0.14 respectively) (Chapter 5). The effect was much smaller than that of maternal illicit drug use, where children born to mothers with reported drug use in pregnancy were significantly lighter, shorter and had a smaller head

circumference than those with no reported drug use (Ross *et al.* 1995). However, uninfected children born prematurely and exposed to combination therapy generally reached a given centile for weight or head circumference earlier, than those in the same gestational age category who were either not exposed or who were only exposed to monotherapy. These findings are consistent with the hypothesised mechanism underlying the increased risk of prematurity with exposure to HAART, that prematurity is mediated through a cytokine balance resulting in premature labour, rather than being due to infant factors (Fiore *et al.* 2006). Although prematurity can be appropriately managed in resource-rich settings, since there is an association between extreme prematurity and infant mortality (European Collaborative Study 2004a) the situation should be monitored.

Malignancies

In the ECS there were no malignancies reported in uninfected children exposed to ART, similar to earlier findings from the PACTG (Culnane *et al.* 1999, Hanson *et al.* 1999) (Chapter 4). In much of the previously published work, only exposure to ZDV has been addressed (Chotpitayasunondh *et al.* 2001, Culnane *et al.* 1999). One of the strengths of the ECS is the large number of uninfected children exposed to combination therapy *in utero*. A limitation of the analysis of adverse health events carried out using data from the ECS was that the median length of follow-up was only just over two years (Chapter 4). Nevertheless, since the analyses presented here were carried out, a longer period of follow-up has been accrued for a substantial number of children (European Collaborative Study 2005b). Other cohort studies such as the French Perinatal Cohort Study and the Women and Infants Transmission Study (WITS) in the USA end formal follow-up around two years of age (Le Chenadec *et al.* 2003, Paul *et al.* 2005).

There were no notifications of cancer registration reported for the 2429 uninfected children who were flagged in the Office for National Statistics (ONS) flagging study (Chapter 6). However the median length of time on the National Health Service Central Register (NHSCR) for these children was only two and a half years. Therefore, observations to date cannot exclude an elevated risk of malignancies, since all the children flagged are relatively young and malignancies may develop at older ages, as was seen with *in utero* exposure to diethylstilbestrol (DES). Clear cell adenocarcinoma of the vagina and cervix was found in young women whose mothers had taken DES in pregnancy which was prescribed to prevent miscarriage and other complications (Schrager and Potter 2004).

9.4 Feasibility of follow-up studies

Research is needed in order to identify whether there are long-term adverse effects of exposure to ART, and cohort studies such as the ECS, the WITS and the French Perinatal Cohort Study, provide an opportunity to do this. Findings from these studies should be used to inform monitoring programmes, which could focus on a small number of health outcomes.

The CHART study was carried out to see if it was feasible to manage a consented clinic-based monitoring system, within the appropriate ethical parameters, at a population level based on reports of children made to the NSHPC (Chapter 7). Just over 2100 children were eligible for enrolment in the CHART study. Of the parents and carers who were actually approached regarding enrolment, nearly 90% agreed to take part, but overall only a third of eligible children were enrolled by the end of the study period. As reporting to the NSHPC is anonymous and there is no direct contact with families, the CHART study was dependent on a network of health professionals which included over

330 individuals by the end of the study period. About a third of eligible children could not be enrolled because the health professional had not been willing to contact the family or there had been no response from the health professional despite reminders. This raises the issue of whether health professionals are the most appropriate channel for long-term follow-up of these generally well children.

The amount of effort that health professionals put into attempting to contact the family about the CHART study before they reported the child as lost to follow-up was variable. Some considered that a child was lost to follow-up if they had been discharged from the paediatric clinic, whereas others reported having tried telephoning or writing to the family, making home visits and accessing other health professionals likely to be in contact with the family.

In some cases a child's uninfected status was reported to the NSHPC after the child had been discharged from the paediatric clinic following a negative antibody test (usually around 12-18 months of age). As the NSHPC paediatric respondent was then no longer in close contact with the family, this made it more difficult for them to approach the parent about enrolment in the CHART study. This was particularly important in situations where the health professional felt they could only speak to the parent about the study at a clinic appointment. Some health professionals also reported that families were lost to follow-up even before the antibody test.

"In retrospect I should have discussed it more regularly at clinic visits but many had only had 1 or 2 negative tests and were indeterminate status. By the time they are known to be negative they are then not in regular contact until 18/12 [18 months] *and many of these are lost to follow up/move."* [Paediatrician]

Health professionals were not paid for their involvement in the CHART study, and lack of resources meant that some were unable to take part at all. The amount of clinic staff time that was available for enrolment and data collection would have varied between hospitals. In some of the large hospitals, dedicated paediatric HIV clinic staff were available to manage the study on a local level. Only a fifth of respondents in the health professional survey reported that lack of clinic staff time was a major factor which made enrolment difficult. An important consideration was the increase in the number of eligible children reported to the NSHPC during the CHART study, which far exceeded that predicted before the start of the study. This was due mainly to the significant increase in the prevalence of HIV infection in pregnant women from 2000 (see Figure 1.5) and also the widespread introduction of routine antenatal testing across the UK also from 2000 (NHS Executive 1999), both of which occurred after the CHART study had been planned. Health professionals in clinics where caseloads increased rapidly over the CHART study period reported difficulties in enrolling children:

"The entire workload has rested with a single paediatric consultant (myself) and the paperwork and parent liaison has been a nightmare. We are a particularly busy unit and a smaller unit with fewer children would find this a lot easier." [Paediatrician]

The most frequently given reason for loss to follow-up of children eligible for enrolment in the CHART study was that the family had moved or changed their contact details: a quarter of eligible children were lost to follow-up or were known to have gone abroad. Similarly, in the PACTG 219 study, a long-term observational study of children enrolled in the PACTG 076 trial, loss to follow-up is estimated to be about 10% per year (Culnane *et al.* 1999). Even among the children who were actually enrolled in the CHART study, 7% were subsequently reported as lost to follow-up within a relatively short space of time.

It was reassuring to find that enrolled and non-enrolled children in the CHART study were similar in terms of their baseline demographic characteristics, which were available through routinely collected data from the NSHPC. However, as enrolment and continued data collection through the CHART study was carried out in an opportunistic way, it is possible that children with more severe or chronic conditions who require continued contact with health services were more likely to be enrolled.

The CHART study demonstrated the difficulties involved in monitoring the health of these children at a population level. It became clear that regular clinic-based contact would not be feasible over the long term or on a national basis. However, it was important to assess this as the protocol was non-invasive, consented and involved health professionals known to the family, and also because both families and health professionals express the opinion that ongoing contact is desirable.

The ONS flagging study highlighted the effectiveness of using routinely collected data to monitor health outcomes in uninfected children exposed to ART (Chapter 6). As long as systems remain in place, notifications of death and cancer registration in flagged children will continue to be reported to researchers at the NSHPC from ONS. The protocol that has been established will make it possible to flag children reported to the NSHPC in future years. Since this process does not require the involvement of health professionals, it is likely to be a relatively inexpensive way of monitoring major outcomes in uninfected children exposed to ART. It is also relatively unbiased in that 95% of eligible children could be flagged, and there were no significant differences in terms of ART exposure between children who were flagged and those who were not.

However, a limitation of the ONS flagging study is that only notifications of death and cancer will be available. Non-fatal clinical symptoms suggestive of mitochondrial abnormalities, such as neurological or cardiac diseases would not be captured through this mechanism (Blanche *et al.* 1999).

The now widespread use of the National Health Service (NHS) number in the UK, coupled with electronic transfer and storage of data, offers new opportunities for data linkage studies (Connecting for Health 2006a). Possible additional data sources that could be linked with data collected in the NSHPC include primary care datasets such as the General Practice Research Database (GPRD) (General Practice Research Database 2006), hospital episode statistics (HES) (Hospital Episode Statistics 2006) and disability and disease registers (Hutchison and Harpin 1998). Clearly, further work would be needed to explore whether these would be viable, as well as research into the health outcomes that should be targeted. The ONS flagging study has support under Section 60 of the Health and Social Care Act 2001 from the Patient Information Advisory Group (PIAG), which enables the collection of patient identifiable information without individual patient consent. New data linkage studies would have to be approached with appropriate ethical and legal consideration.

9.5 Acceptability of follow-up studies

Almost all respondents in the parent and carer survey were supportive of the rationale for follow-up, and while expressing a preference for certain strategies, generally did not dismiss others (Chapter 8). Whether respondents found a particular follow-up strategy acceptable was not generally associated with demographic characteristics. It is likely that factors such as confidence, confidentiality concerns, anxiety about discrimination and

acceptance of HIV diagnosis (if infected) are related to an individual's preference for follow-up strategies.

Contradictory views were expressed both within and between individuals, particularly with respect to whether and how contact should be maintained, and it would be impossible to select one particular strategy which would suit all individuals involved. Individual opinions sometimes reflect confusion and bias (Wendler 2006) and it would be extremely challenging to decide which opinions were "correct".

Clinic-based contact was found acceptable by most respondents, which could reflect the fact that it is familiar to them, but could also be indicative of the age of their children. A clinic that has provided services for the family, possibly over several years, is likely to also provide the reassurance that respondents would not feel in a different situation (Sharland *et al.* 2003, Boulton *et al.* 1999). In a survey of parents of hepatitis C infected children, the favourable option for long-term follow-up of children was for them to continue to see a paediatrician and then transfer to adult care at an appropriate time. This was in preference to ongoing postal or telephone contact (Personal communication, L Pembrey, 2006). A third of respondents in the health professional survey strongly objected to clinic-based contact, citing concerns about confidentiality, the mobility of HIV-affected families and a lack of clinic resources (Chapter 8).

Despite reassurances that no reference to HIV would be made on any literature, one in 10 respondents to the parent and carer survey strongly objected to postal contact (Chapter 8). Health professionals involved in the CHART study also reported that some HIV-affected families do not give permission for letters to be sent home (Chapter 7). This is mainly due to confidentiality concerns, particularly when families are living in shared

accommodation or when the HIV infected woman's family or partner is unaware of her HIV status.

"Problem with postal contact is that may be opened by another family member- many asylum seekers in multi-occupation. Even if no mention of HIV it may trigger awkward questions." [Paediatrician]

Concern about long-term follow-up having the potential to lead to disclosure of maternal HIV status to the child, was raised by some respondents to the parent and carer survey. In a European multi-centre survey, which included some ECS centres, around 10% of HIV infected parents had told their children about their HIV diagnosis (Thorne *et al.* 2000). Disclosure of parental HIV status has been shown to be associated with the increased age of the child, the increased length of time since the parent's HIV diagnosis and the severity of the parent's illness (Lee and Rotheram-Borus 2002, Thorne *et al.* 2000, Nostlinger *et al.* 2004). In a cohort of children born to HIV infected mothers in the UK, infected children were more likely to know their mother's diagnosis than uninfected children (Mok and Cooper 1997), but this has not been observed in other settings (Thorne *et al.* 2000). The disclosure process is complex, and is likely to involve more personal factors such as the existing relationship between the parent and child, anticipated stigma and uncertainty about the future. There is also the consideration of how life events, such as morbidity, may alter opinions. The following statements from HIV infected mothers show the diversity of views held on disclosure:

"I think once a teenager reaches a certain age I not sure I would tell my children I have HIV if I'm still alive so I would not want to harm or scare them in any way but that's a long way ahead of me, things change." [Mother of two children (aged 2 and 4 years)]

"I think it should be up to the parent to tell the clinic if they can contact the young person as it would necessitate the mother's disclosure of her own HIV status and this is a very personal, individual matter." [Mother of one child (aged 1 year)]

"I think that is important to do a follow up, but at the same time if the child is uninfected it is difficult for them to maybe accept or understand about all this, so would be better to leave this subject (or burden as it is at the moment) out of their life." [Mother of one child (aged 2 years)]

Long-term follow-up strategies that are dependent on disclosure are likely to encounter difficulties on an individual level. If health risks to an ART-exposed individual can be screened for or treated, this raises the issue of whether disclosure of maternal HIV status and the fact that the young person was exposed to ART should occur regardless of parental consent. There needs to be a discussion on balancing the rights of the HIV infected mother to privacy and confidentiality, and the rights of the ART-exposed child or adult to appropriate screening or care as appropriate. This should occur within a broad population perspective, rather than on an individual case basis.

The majority of respondents thought that parents and carers should be told of a health problem associated with exposure to a particular antiretroviral drug, which suggests the importance that parents attach to information about their child's health (Thorne *et al.* 1999) (Chapter 8). Nevertheless, actually carrying this out would be challenging, particularly as in some individuals there were inconsistencies between the types of follow-up strategies they found acceptable and how they would want to be contacted. The type of information communicated to the family would have to be decided, such as whether findings from research were provided or whether they were only contacted if screening could be offered to the ART-exposed child or young adult.

A quarter of respondents in the parent and carer survey and half of the respondents in the health professional survey found data linkage acceptable. Two thirds of parents thought that parental permission should be sought before a child was included in any monitoring system relying on data linkage. In the Millennium Cohort Study (MCS), a UK cohort of

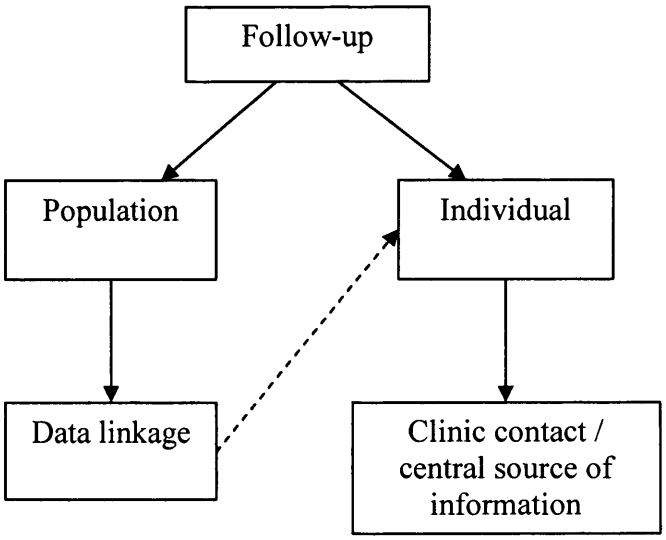
nearly 19 000 children born 2000-2002 which over-sampled from disadvantaged and ethnic minority localities, consent for linkage to birth register and/or hospital maternity data was obtained from over 90% of mothers. However, consent was less likely among minority ethnic group mothers (Tate *et al.* 2006). Although HIV infected mothers are likely to be different in terms of their views regarding confidentiality, the finding from the MCS could have implications for data linkage studies of uninfected children in the UK that involved parental consent, as currently the majority of their mothers are of non-white ethnicity.

The median age of the children of the respondents in the parent and carer survey was two years, which limits the extension of the findings to parents with older children (Chapter 8). The low attendance rate in the paediatric clinics involved in the survey is consistent with the large number of children who were reported as lost to follow-up in the CHART study due to non-attendance (Chapter 7). It also demonstrates the difficulty in accessing HIV-affected families for the purposes of this survey, and indeed any follow-up strategy that relies on clinic attendance. Furthermore, families who attended clinics and therefore were available to take part in the survey could have been more compliant than those who did not attend, which could have introduced selection bias to the survey.

9.6 Recommendations

In the UK, follow-up of ART-exposed uninfected children born to HIV infected women should take place both on an individual level and a population-based level (see Figure 9.1).

Figure 9.1 A general model for the follow-up of uninfected children exposed to antiretroviral therapy



Individual level

Clinic contact

- The child should attend the paediatric clinic for blood tests and assessments up to 18 months of age, as recommended in the British HIV Association pregnancy guidelines (Hawkins *et al.* 2005)
- Paediatric clinic staff should encourage the parent/carer to stay in touch with the clinic once their child has been confirmed uninfected, and to contact the clinic if they have any concerns about their child's health

- Paediatric clinic staff should support the parent/carer in disclosing the mother's HIV status and the child's ART exposure to both relevant health professionals, and to the child when they are of an appropriate age
- GU clinic staff should take an active role in supporting the parent in the disclosure process

Central source of information for families

- There should be a central source of information for families with ART-exposed children
- Information provided should include: findings from research into possible adverse side effects of ART exposure, how the parent/carer or the ART-exposed individual could report any adverse side effects, details of support groups and clinical care for HIV-affected families, and advice on how to disclose the mother's HIV status and the child's ART exposure to both relevant health professionals and to the ART-exposed individual
- This resource could be accessed through telephone or postal contact or from a website; and details should be provided to the woman during her own care and during her child's paediatric follow-up
- This resource could be incorporated with information about other drug exposures in pregnancy, in an attempt to normalise maternal HIV infection and the child's ART exposure

Population-based level

- Children born to HIV infected women in the UK should be reported to the NSHPC, as recommended in the British HIV Association pregnancy guidelines (Hawkins *et al.* 2005)

- The ONS flagging study should continue
- The feasibility of using other routine data sources that could be linked to data collected in the NSHPC, should be explored
- A data linkage study should contain the facility to contact the family or the ART-exposed individual should a significantly increased risk of a serious condition be identified. Contact would have to be approved through the appropriate channels, be subject to strict data security measures and would only be used for serious conditions where there was an appropriate screening tool or treatment available

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Appendix 1 The European Collaborative Study

Collaborators

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Appendix 2 The European Collaborative Study forms

2.1 Maternal information

2.2 Perinatal information

2.3 Laboratory investigations

2.4 Medical examination

2.5 Assessment

ECS3
INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

MATERNAL INFORMATION AT DELIVERY

Centre
Mothers Study Number
Child Study Number

Mother's date of birth (day, month, year)
Country of birth .....

Marital Status

Single (1), Married (2), Divorced, Separated, Widowed (3), Cohabiting (4)

Ethnic Group

Asian (1), White (2), Black (3), Oriental (4), Other (5)
Age when leaving full-time education, years .....

Obstetric History

Number of previous livebirths .....
Number of previous stillbirths .....
Number of previous miscarriages .....
Number of previous terminations .....

Mothers Risk Group

History of intravenous Drug Abuse (Y/N)
Trimester of last use: pre-conception (0), 1st (1), 2nd (2), 3rd (3), unknown (9)
Needle sharing? never (1) past (2) present (3) unknown (9)
Sexual partner of Bisexual (Y/N)
Sexual partner of Haemophiliac (Y/N)
Sexual partner of Intravenous Drug Abuser (Y/N)
Sexual partner of Other high risk group (Y/N)
(Specify) .....
Other .....

Mothers HIV History

Date of first HIV+ test (day, month, year)

Current clinical status

Current HIV staging (CDC) .....
Specify symptoms .....
Date of onset .....

Details of treatment during pregnancy

Has the woman received any antiretroviral therapy at any time during this pregnancy? Y/N
Please give details of both ART and other prophylaxis (eg. TMP-SMX)

Drug	Date started	Date stopped	Currently taken? (yes/no)

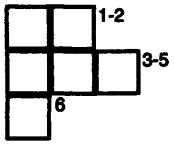
ECS 3
PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

Page 2

MATERNAL INFORMATION

Laboratory investigations during pregnancy and at delivery:

Centre Number
Mothers Study Number
Child Study Number



Virology

	Date:	Date:	Date:
HIV-DNA PCR	Pos / Neg	Pos / Neg	Pos / Neg

HIV-RNA PCR	copies/ml	copies/ml	copies/ml
Sample type	Plasma / Serum	Plasma / Serum	Plasma / Serum
Assay used			

Other laboratory investigations

	Date:	Date:	Date:
Total lymphocytes			
CD4 (10^9/litre)			
CD8 (10^9/litre)			
IgG (gm/litre)			
IgA (gm/litre)			
IgM (gm/litre)			
p24 Ag			
HIV Elisa			

ECS3
INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

PERINATAL INFORMATION

Centre
Mothers Study Number
Child Study Number
Child's date of birth (day, month, year)
Sex (M, F)
Gestational age (weeks)
Birthweight (gm)
OFC (cm

Hospital where delivery took place .....
Obstetrician (initals) .....
Antiretroviral therapy during labour/delivery Y/N
If yes, which drug? .....Orally / IV?
Delivery
Caesarean Section: Elective (1), Emergency (2)
If Caesarean Section, reason.....
Vaginal: Spontaneous (3), vacuum (4), forceps (5)
Presentation: breech (Y/N)
Duration of labour 1st stage (if known).....
Duration of labour 2nd stage (if known) .....
Time from rupture of membranes to delivery (if known).....
Scalp Electrodes (Y/N)
Episiotomy or vulvovaginal tear (Y/N)
Perinatal Problems (Y/N). Specify Details:
Hepatomegaly .....
Splenomegaly .....
Drug Withdrawal Symptoms .....
Thrombocytopenic Purpura .....
Infection: suspected (1) confirmed (2) .....
Transfusion ..... *
Congenital Abnormalities ..... *
Other .....
Disposition
with parents (1) fostered (2) adopted (3)
remained in hospital (4) other (5) ..... *
if remained in hospital, say why: .....
Feeding: breast (1) bottle (2) breast and bottle (3)
was breast feeding tried and abandoned? Y/N
Died? Y/N
Date of death: (day/month/year)
Postmortem results, if available ..... *
.....

Take sample required; Please record laboratory results on yellow form

9 2

PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS

Centre 1-2
Mothers Study Number 3-5
Child Study Number 6

LABORATORY INVESTIGATIONS

Assessment at:
0-7 days, 3w, 6w, 4.5m, 6m, 9m, 12m, 18m, 24m, and then annually if child presumed not infected, or 6 monthly if infected

Ring findings and specify as appropriate:

for office use only

Date blood drawn: _____ / _____ / _____ 7-12
day month year

HIV / ELISA + / - Specify system used 13-14
antibodies 15-16

Western blot + / - 17-18

Virus culture
+ / - Specify identification system(s) 19-20
+ / - Specify identification system(s) 21-22

Viral load
DNA - PCR 23-24
RNA - PCR 25-26

Antigen assay + / -
Specify identification system 27-29

Other tests (eg IVAP, PCR, IgM) Specify method and result
+ / - 30-32
+ / - 33-35

IgG (gm/litre) 36-38
IgA (gm/litre) 39-41
IgM (gm/litre) 42-44
T4 (10^9/litre) 45-48
T8 (10^9/litre) 49-52
Absolute lymphocyte (10^9/litre) 53-56
Neutrophil (10^9/litre) 57-60
Platelet (10^9/litre) 61-64
Haemoglobin (gm/dl) 65-67

Toxo IgG Latex (at 9 months to exclude congenital infection) (+/-) 68
Tetanus IgG (at least 1 month after third DT/DPT) 69-71
CMV IgG (+/-) 72

8 1 73-74

ECS3

INTENSIVE PROSPECTIVE STUDY OF CHILDREN BORN TO HIV POSITIVE MOTHERS
MULTI CENTRE EEC STUDY

MEDICAL EXAMINATION

Please circle or complete as appropriate

Assessment at : 3w, 6w, 3m, 4.5m and 6 m

Centre 1-2
Mothers Study Number 3-5
Child Study Number 6
Date of Examination 7-12
Weight (kg) 13-16
Height (cm) 17-20
OFC (cm) 21-23

24 **For office use only**

Recurrent fever of unknown origin requiring medical attention .....Y/N 25
Chronic or Recurrent diarrhoea requiring medical attention .....Y/N 26
Specify organism 27
Bacterial infection .....Y/N 28-30
If yes, specify:
Septicaemia, Meningitis, Urinary tract infection, Pneumonia, Other 31-33
Communicable Disease .....Y/N
Measles (1) Mumps (2) Rubella (3) Varicella (4) Zoster (5) Other (6) 34-35
Complications .....
Skin Infection requiring medical attention .....Y/N 36-38
Staph (1) Strep (2) Herpes (3) Candida (4) Other (5) .....
Non-infectious skin eruption .....Y/N 39
Petechiae/Purpura (1) Eczema (2) Kaposi Sarcoma (3) Other (4) 40
Palpable Lymph Nodes .....Y/N 41-43
Axillary (1) Postoccipital (2) Cervical (3) Inguinal (4) Epitrochlear (5) Other (6) 44-46
Chronic parotid swelling .....Y/N 47
Oral Candida persistent or recurrent despite therapy .....Y/N 48
Upper respiratory tract infection .....Y/N
Chronic otitis media (1) Sinusitis (2) Chronic purulent rhinitis (3) Other (4)..... 49-50
Lower respiratory tract disease confirmed by X-ray.....Y/N
Lymphocytic intersitial pneumonitis or Pulmonary lymphoid hyperplasia (1)
Pneumonia (2) Bronchiolitis (3) Other (4) 51-53
specify organism, if known.....
Opportunistic Infection .....Y/N 54
PCP (1) CMV (2) Toxo (3) Candida (4) Mycobacterium (5) Other (6) .....
Hepatomegaly.....Y/N 55
Splenomegaly.....Y/N 56

7 1 57-58

Please circle or complete as appropriate

Medical Examination

Date of Examination ___ / ___ / ___

Centre 1-2

Mothers Study Number 3-5

Child Study Number 6 7

For office use only

Neurological abnormality ..... Y/N 8-10

encephalopathy (static/progressive) (1) 11-13

seizures (2) paresis (3) pathologic reflexes (4) increased tone (5)

decreased tone (6) abnormal gait (7) other (8) 14-16

Other Findings on exam Specify ..... Y/N 17

Developmental Asessment

Gross motor	Pass (1) Fail (2) Suspicious (3)	18
Fine motor/adaptive	Pass (1) Fail (2) Suspicious (3)	19
Language	Pass (1) Fail (2) Suspicious (3)	20
Personal/social	Pass (1) Fail (2) Suspicious (3)	21

Loss of developmental milestones ..... Y/N 22-23

specify .....

Neonate

Has the baby received any anti-retroviral therapy to reduce

the risk of vertical transmission? ..... Y/N 24

If yes: which drug(s)? 25-26

for how long? 27

Treatment

Has this child been enrolled in an anti-retroviral treatment trial ..... Y/N 28

If yes: which trial? 29-31

Current treatment (excluding the above)

IVGG, AZT, DDi, Other 32-36

37-41

Hospital Admission(s) ..... Y/N 42

(Indicate dates of admission/discharge and diagnoses for each hospitalization)

..... 43-46

..... 47-50

Immunisations given since last visit ..... Y/N

DPT (1) DT(2) Oral Polio (3) Killed Polio (4) Measles (5) MMR (6) 51-52

Hepatitis B (7) Other (8) 53-54

Abnormal reactions ..... Y/N 55

Child care

mother / father / other relative / fostered / adopted / hospital / institution

Breast Feeding ..... Y/N 56

If stopped, when 57-58

Health of Mother .....

Is mother alive / dead? 59

if dead, was death HIV-related? ..... Y/N 60

cause of death 61

Mother's current HIV staging (CDC) 62-63

defining symtoms 64-68

date of diagnosis 69-73

current treatment? 74-75

8 2 76-77

ECS.1
PROSPECTIVE STUDY OF CHILDREN BORN TO HIV +VE MOTHERS

<u>Assessment:</u> 9, 12, 18 and 24 months; thereafter annually for antibody -ve, uninfected children and 6-monthly for infected children

Please circle or tick as appropriate

Centre number [1-3]
Mother Study number [4-6]
Child Study number [7]
Weight (kg) [8-11]
Height (cm) [12-15]
Head circumference (cm) [16-18]

Is child alive? Y/N [19] **For office use only**
Date of assessment (day, month, year) . . . . . [20-25]

Name of paediatrician (initials) . . . . . [26-27]

Is this child HIV infected? . . . . . Y/N [28]
Has this child developed AIDS? (CDC def) . . . . . Y/N [29]
If AIDS has been diagnosed since previous report,
specify date of diagnosis . . . . . [30-35]
AIDS indicator disease . . . . . [36-38]

Care
mother / father / other relative / fostered / adopted / hospital / institution [39]

Is mother alive / dead?
if dead, was death HIV-related? . . . . . Y/N [40]
cause of death . . . . . [41]

Preschooling/Schooling
Does this child require special educational provisions . . . . . Y/N [42]
if yes, specify . . . . . [43-44]

Treatment
Has this child been enrolled in an anti-retroviral treatment trial . . . . . Y/N [45]
if yes, which trial? . . . . . [46-48]
Current treatment (excluding the above) . . . . . [49-53]
Intravenous gammaglobulin/AZT/DDi/other, specify . . . . . [54-58]
. . . . . .

Communicable diseases . . . . . Y/N [59]
if yes, specify: measles / whooping cough / varicella / tuberculosis / mumps / zoster

G 2 1 [60-62]

ECS .1 **(page 2)** Centre ..... Mother ..... Child ..... Date ...../...../.....

Oral Candida since last visit (persisting > 2m or recurring despite therapy) Y / N

if yes, date on onset (day, month, year) .....

Hospital admission(s) Y / N

(indicate dates of admission/ discharge and diagnoses for each hospitalization)

.....

Since the last visit, has this child had any of the following abnormalities:

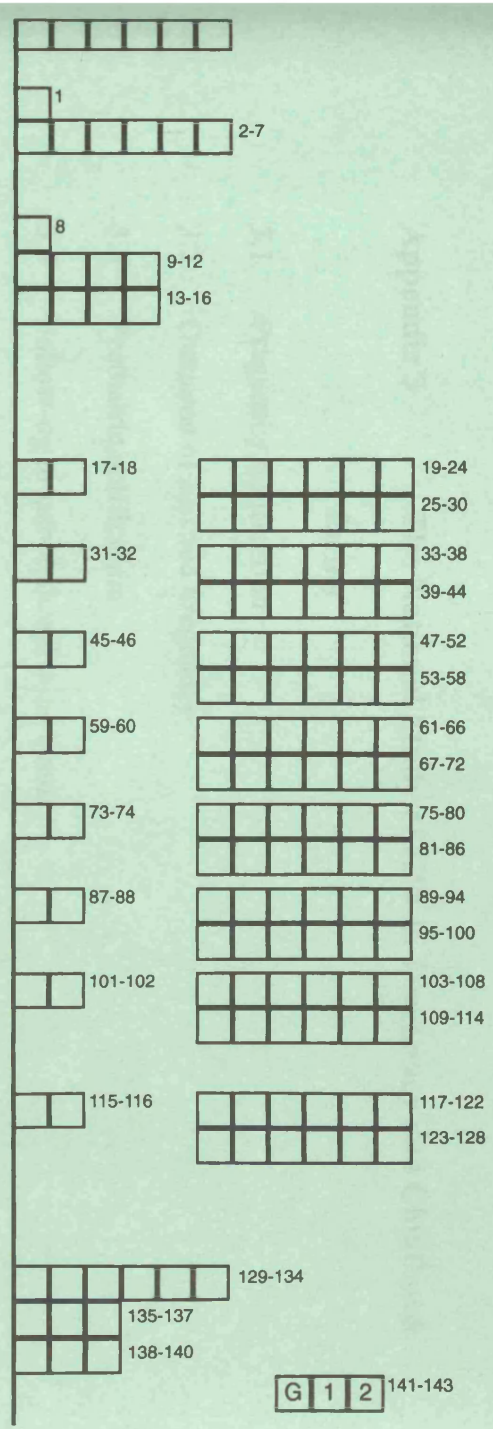
	yes/no	date	clinical presentation	method of diagnosis	diagnosis
renal	Y / N	.....			
hepatic	Y / N	.....			
gastro-intestinal	Y / N	.....			
cardio-vascular	Y / N	.....			
central nervous system	Y / N	.....			
respiratory	Y / N	.....			
malignancy	Y / N	.....			
other, specify	Y / N	.....			

Please complete this section, if the child has died

Date of death .....

Cause of death .....

Post mortem results .....



Appendix 3 The National Study of HIV in Pregnancy and Childhood forms

3.1 Pregnancy notification

3.2 Outcome of notified pregnancy

3.3 Paediatric notification

3.4 Follow-up to establish infection status

NSHPC confidential pregnancy notification

MREC approval ref: MREC/04/2/009

CONFIDENTIAL
Tick boxes, complete, ring, or delete as appropriate

form date 01/05

Hospital ..... Your ref (eg woman's hospital number, local code or soundex) .....

Woman's date of birth ___/___/___ Previous livebirths ..... stillbirths ..... miscs/terms .....

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black other
☐ Indian Subcontinent ☐ Oriental ☐ Other or mixed, specify .....

Country of birth..... Current postcode of residence (leave off last letter) ☐☐☐☐ ☐☐■

PREGNANCY LMP ___/___/___

☐ Continuing to term EDD ___/___/___

☐ Spontaneous abortion *or* ☐ termination on ___/___/___ at ..... weeks gestation

If spontaneous abortion or termination, any congenital abnormality? ☐ No ☐ Yes Please specify overleaf

Were antenatal booking bloods taken at this maternity unit? ☐ No ☐ Yes

PROBABLE SOURCE OF INFECTION

☐ From high prevalence country, specify ..... Date arrived UK/Ireland ___/___/___

☐ Injecting drug use ☐ Transfusion recipient ☐ Other, specify .....

☐ Infected partner, specify his likely risk factor .....

INFECTION STATUS IDENTIFIED

☐ During this pregnancy: voluntary antenatal testing / other setting, specify .....

☐ Known prior to this pregnancy: tested at GUM Clinic / GP / Drug Clinic / other .....

Date of first positive test ___/___/_____ If type 2 only, please tick here ☐

CLINICAL STATUS & DRUG TREATMENT DURING PREGNANCY

☐ Asymptomatic ☐ Symptomatic, not stage C disease ☐ CDC Stage C disease, date of onset ___/___/___

Details .....

Was this woman on drug treatment when she became pregnant? ☐ No ☐ Yes Started ___/___/___

If **Yes**, specify drug(s) ..... Continuing? ☐ No ☐ Yes

..... Date stopped ___/___/___

Drug treatment changed or started during pregnancy?

☐ No ☐ Not yet decided ☐ Drug treatment declined ☐ Yes, changed or started, details below:

Drug(s) ..... Date started or

..... due to start ___/___/___

RECENT TEST RESULTS

Viral load ..... copies/ml (..... log_{10}) test ..... Date ___/___/___

CD4_____% no._____ CD8_____% no._____ Total lymphocytes no. _____ ___/___/___

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email _____

PLEASE ADD ANY ADDITIONAL INFORMATION OR COMMENTS OVERLEAF.

NSHPC outcome of notified pregnancy

MREC approval ref: MREC/04/2/009

CONFIDENTIAL
Tick boxes, complete, ring, or delete as appropriate

form date *01/05*

Your ref ..... Woman's date of birth ___/___/___ Hospital of delivery .....

PREGNANCY OUTCOME

Date ___/___/___ Gestation ..... (wks) ☐ Livebirth ☐ Stillbirth ☐ Miscarriage ☐ Termination

Birthweight ..... (kg) ☐ Male ☐ Female Hospital no ..... NHS no .....

2nd twin: BW ..... (kg) ☐ Male ☐ Female Hospital no ..... NHS no .....

☐ Elective CS ☐ Planned vaginal delivery ☐ Unplanned vaginal delivery, reason .....

☐ Emergency CS, reason .....

Complications: Pregnancy (eg pre-eclampsia)? ☐ No ☐ Yes, specify .....

Perinatal infections? ☐ No ☐ Yes, specify .....

Congenital abnormalities? ☐ No ☐ Yes, specify .....

Postcode at delivery (leave off last letter) ☐☐☐☐ ☐☐■ Paediatrician .....

MATERNAL CLINICAL STATUS AT DELIVERY

if woman has died,

☐ Asymptomatic ☐ Symptomatic, not stage C disease ☐ CDC Stage C disease Date of death ___/___/___

Details .....

DRUG TREATMENT DURING PREGNANCY (if not enough space for all drugs, continue overleaf)

Ante-partum treatment? ☐ No ☐ Yes: date started (or gest week) date stopped (or gest week)

Antiretrovirals:

Drug 1	___/___/___	_____	___/___/___	_____
Drug 2	___/___/___	_____	___/___/___	_____
Drug 3	___/___/___	_____	___/___/___	_____
Drug 4	___/___/___	_____	___/___/___	_____
Drug 5	___/___/___	_____	___/___/___	_____

Any other significant ante-partum drugs (eg PCP prophylaxis, TB treatment, prescribed methodone, illicit drugs)

Drug 6	___/___/___	_____	___/___/___	_____
Drug 7	___/___/___	_____	___/___/___	_____

Intra-partum antiretroviral treatment?

☐ None ☐ Oral ..... ☐ Intravenous Drug(s) .....

Post-partum antiretroviral(s) for **infant**? ☐ No ☐ Yes ☐ Not known

If **yes**, date treatment started ___/___/___ Drug(s) .....

MATERNAL TEST RESULTS CLOSE TO TIME OF DELIVERY *just before delivery if possible*

Viral load ..... copies/ml Test ..... Date ___/___/___

CD4_____% no._____ CD8_____% no._____ Total lymphocytes no. _____ ___/___/___

Form completed by: Name _____ Date ___/___/___

Position _____ Telephone _____ Email

NSHPC confidential paediatric notification

LONDON MREC/04/2/009

office use only *May 2005*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician _____ **Hospital** _____

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

A PAEDIATRIC DETAILS

NHS no ..... Hospital no ..... Initials ..... Soundex .....

Date of birth ___/___/___ ☐ Male ☐ Female Home postcode *(leave off last letter)* ☐☐☐☐ ☐☐■

Ethnic origin ☐ White ☐ Black African ☐ Black Caribbean ☐ Black other
☐ Indian Subcontinent ☐ Oriental ☐ Other or mixed, specify .....

Born in ☐ UK/Ireland Hospital of birth ..... Home postcode at birth *(leave off last letter)* ☐☐☐☐ ☐☐■
or ☐ Abroad Country of birth ..... and date arrived in UK/Ireland ___/___/___

B HOW WAS THIS CHILD IDENTIFIED AS INFECTED OR AT RISK OF INFECTION?

☐ Mother known to be infected in pregnancy ☐ Child symptomatic
☐ Mother/other family member found to be infected (specify relationship) .....
☐ NK ☐ Other, specify .....
Date of child's first lab investigation ___/___/___ ☐ not yet done ☐ tests refused ☐ NK
If you are aware of *siblings* reported to us, please give dates of birth or other ref: .....

C PERINATAL DETAILS

Mode of delivery ☐ vaginal ☐ elective CS ☐ emergency CS ☐ NK **Gestation** ..... **Birthweight** .....

Any perinatal infections? ☐ No ☐ Yes, specify .....
Any congenital abnormalities? ☐ No ☐ Yes, specify .....
Any other problems? ☐ No ☐ Yes, specify .....

Anti-retroviral treatment for mother and/or baby to reduce risk of vertical transmission? ☐ No ☐ Yes, specify below
Antenatally? ☐ NK ☐ No ☐ Yes, specify .....
Intrapartum? ☐ NK ☐ No ☐ Yes, specify .....
Post-partum (baby)? ☐ NK ☐ No ☐ Yes, specify .....

Was the child breastfed? ☐ No ☐ Yes, and breastfed for how long? (wks) ..... ☐ NK if breastfed

D PROBABLE SOURCE OF INFECTION

1. Exposed to maternal infection? ☐ Yes, please give *mother's* details below ☐ No, go to question 2 below ☐ NK

a) Mother's date of birth ___/___/___ b) No. of *previous* livebirths..... stillbirths..... miscarriages/terms.....
c) Mother's country of birth ..... and if not UK/Ireland, date arrived ___/___/___
d) Mother diagnosed ☐ after the birth of this child ☐ while pregnant with this child ☐ before this pregnancy
e) Maternal infection probably acquired ☐ in UK/Ireland ☐ abroad, specify ..... ☐ NK where and likely exposure (tick all that apply)
☐ injecting drug use ☐ transfusion recipient
☐ sexual exposure, specify partner's probable risk factors if known .....
☐ mother to child transmission ☐ no information on mother's exposure

2. Other exposure risk for child? ☐ No ☐ Yes, please give details
☐ blood/blood products abroad, please specify country and year .....
☐ sexual exposure ☐ other, please specify.....

Thank you for completing the attached form. Please return it in the freepost envelope to:
Surveillance Studies Group, Centre for Paediatric Epidemiology & Biostatistics, Institute of Child Health, 30 Guilford St, London WC1N 1BR.

If you have any queries phone us on 020 7829 8686.

Please complete this box and keep this page for your own records to help identify the child when you receive a follow-up form

Child's name or other identification .....

Hospital number ..... Study number (CSTU) .....

INFECTION STATUS

INFECTED

a) definitive

1. Child has Stage C disease (see definitions overleaf)
2. The detection of virus by PCR (at any age) on two separate specimens taken at different times
3. Antibody positive after the age of 18 months, or at any age if not born to an infected woman

b) presumptive

The detection of virus by PCR (at any age) on one occasion

NOT INFECTED

a) definitive

Any one of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test after the age of 12 months
2. Two consecutive negative antibody tests on separate samples taken at different times in children under 12 months
3. Two separate, consecutive, negative PCR results after one month of age – at least one of these to be after 3 months of age
4. One negative PCR result and one negative antibody test on separate occasions after the age of 3 months

b) presumptive (in a non-breastfed child)

Either of the following and no evidence (viral, immunological or clinical) of infection:

1. One negative antibody test under the age of 12 months
2. One negative PCR after the age of one month

Indeterminate

A child born to an infected woman where the child's own infection status is not yet determined

Definitions of specific manifestations of infection requested

Manifestation	Definition
Asymptomatic LIP* (see overleaf for definition of LIP)	CXR abnormalities only; no respiratory signs or symptoms
Severe bacterial infection	Single severe bacterial infection (state how diagnosed)
Failure to thrive	Failure to thrive, not yet meeting definition overleaf
Regression of developmental milestones	Consistent regression over at least 3 months

P.T.O. for definitions of Stage C indicator diseases

NSHPC follow-up to establish infection status

MREC ref: MREC04/2/009

office use only *July 2005*

CSTU	MSTU	SU	PAED	HOSP

Paediatrician ..... Hospital .....

CONFIDENTIAL Please complete this form as far as you can, even if you do not have all details requested

Please complete or amend these child details

Date of birth ___/___/___ ☐ Male ☐ Female Initials ..... soundex if available .....

Hospital no..... NHS no..... Current home postcode **(leave off last letter)** ☐☐☐☐ ☐☐■

The last report we had on this child related to examination on ___/___/___ when his/her **infection status had not yet been confirmed**. If you have more recent information, please complete all sections of this form.

If you have not seen this child since the last report please tick here ☐, complete the section on **INFECTION STATUS**, provide any test results *not previously reported* and complete the section on **FOLLOW UP STATUS.**

INFECTION STATUS & LABORATORY INVESTIGATIONS

Do you consider this child to be ☐ infected ☐ not infected ☐ indeterminate (definitions overleaf)

Please provide date of sample and ring type of test and result for all diagnostic tests since ___/___/___

	sample date	type of test	result		sample date	type of test	result
1.	___/___/___	antibody / PCR	+ / -	4.	___/___/___	antibody / PCR	+ / -
2.	___/___/___	antibody / PCR	+ / -	5.	___/___/___	antibody / PCR	+ / -
3.	___/___/___	antibody / PCR	+ / -	6.	___/___/___	antibody / PCR	+ / -

NB If this child is now known to be infected we will contact you again for information on viral load, T-cell subsets and antiretroviral therapy.

THERAPY & CLINICAL DETAILS

PCP prophylaxis? ☐ No ☐ Yes, specify ..... date started ___/___/___

Date of last examination ___/___/___ *and, if taken at that time:* Weight (kg) ..... Height (cm) .....

Any other serious infections or conditions? ☐ No ☐ Yes, specify .....

FOLLOW UP STATUS

Date of last contact ___/___/___ ☐ Alive ☐ Lost to follow up ☐ Known to have left UK/Eire

☐ Being seen elswhere (please give details overleaf) ☐ Dead, date of death ___/___/___ and if dead

Certified cause of death a) disease or condition directly leading to death .....

b) secondary cause(s) .....

Post-mortem? ☐ Not done ☐ Done. Please attach a copy if possible.

Completed by: Name _____ Position _____ Date ___/___/___

Tel no _____ Email _____

Appendix 4 The Office for National Statistics flagging study: tables and figure

4.1 Matches made when the matching algorithm was used without NHS number as compared to type 1 matches made when it was used with NHS number: unique matches and no matches

4.2 Matches made when the matching algorithm was used without NHS number as compared to type 1 matches made when it was used with NHS number: multiple matches

4.3 Confirmation of matches made using the matching algorithm

4.1 Matches made when the matching algorithm was used *without* NHS number as compared to type 1 matches made when it was used *with* NHS number: unique matches and no matches (n=134)

Matches *without* NHS number	Subjects (n)	Reason for unique incorrect match/no match	Confirmation of correct/incorrect match without NHS number: do MCOB, BWψ and PCD agree? (subjects)
Unique *correct* match on type 2	121	-	Agreed on 3 variables (53) Agreed on 2 variables and 1 input variable missing (34) Agreed on 2 variables and disagreed on 1 variable (12) Agreed on 1 variable and 2 input variables missing (12) Agreed on 1 variable, disagreed on 1 variable and 1 input variable missing (8) Agreed on 1 variable and disagreed on 2 variables (1) Disagreed on 1 variable and 2 input variables missing (1)
Unique *correct* match on type 4#	5	-	Agreed on 2 variables (3) Agreed on 1 variable and 1 input variable missing (1) Agreed on 1 variable, disagreed on 1 variable and 1 input variable missing (1)
Unique *incorrect* match on type 2	4	Input MDOB differed from output MDOB on type 1 with NHS number	Disagreed on 3 variables (2) Disagreed on 2 variables and 1 input variable missing (2)
Unique *incorrect* match on type 3	2	Input MDOB differed from output MDOB on type 1 with NHS number	Disagreed on 2 variables and 1 input variable missing (1) Disagreed on 2 variables and agreed on 1 variable* (1)
Unique *incorrect* match on type 4#	1	Input MDOB and PCD differed from output MDOB and PCD on type 1 with NHS number	Disagreed on 1 variable and 1 input variable missing (2)
No match	1	Input PCD and MDOB missing	-

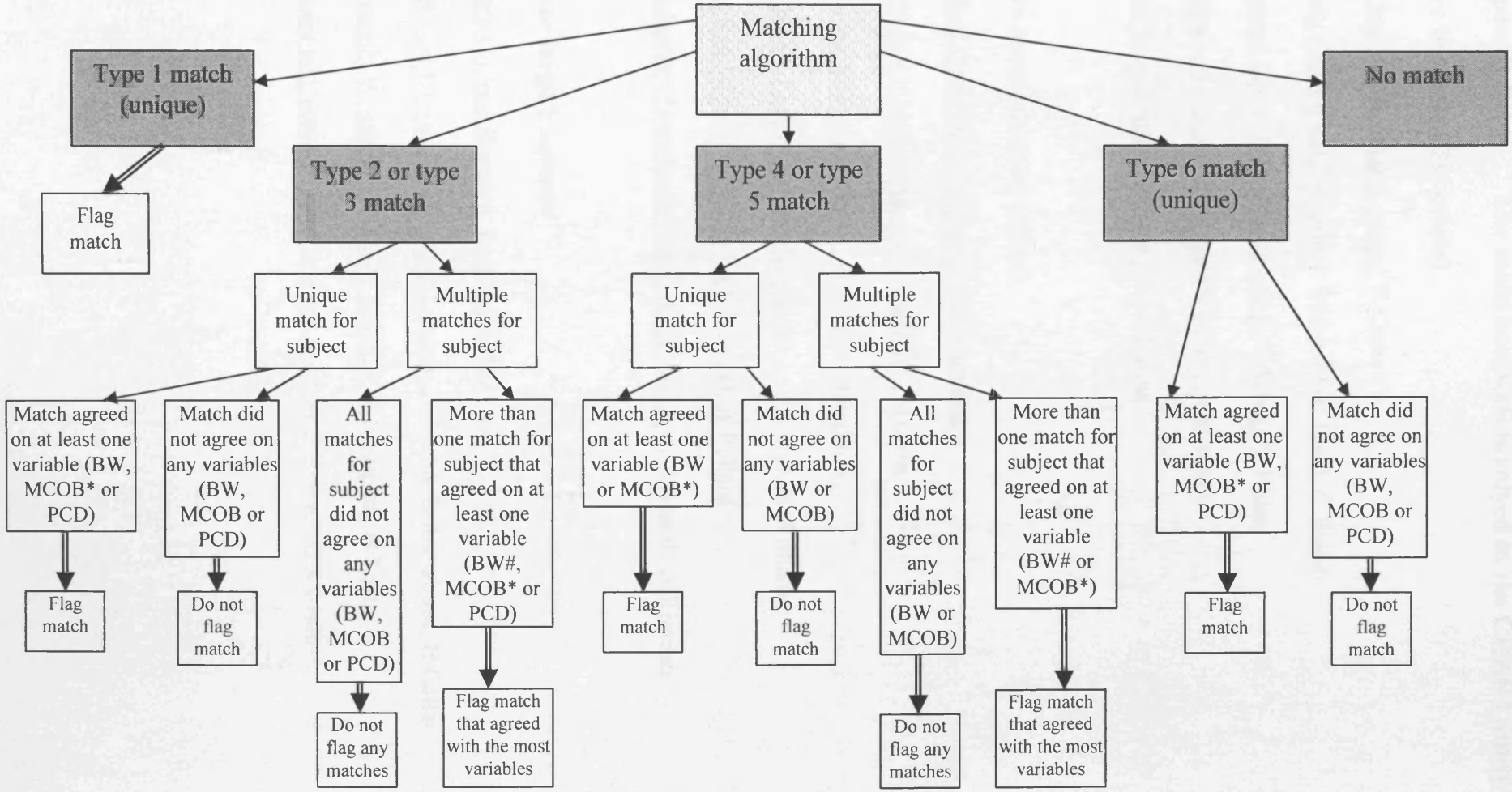
Notes: MDOB, mother's date of birth; PCD, mother's postcode district of residence at delivery; MCOB, mother's country of birth; BW, child's birth weight. Matches were identified as correct/incorrect if NHS number of the match found with the algorithm used without NHS number was the same/different as that found with the algorithm used with NHS number. *MCOB was UK. #Type 4 match includes PCD, therefore not included in the confirmation of correct/incorrect match. ψ within 10g.

4.2 Matches made when the matching algorithm was used *without* NHS number as compared to type 1 matches made when it was used *with* NHS number: multiple matches (n=32)

Matches *without* NHS number	Subject (n)	Confirmation of correct/incorrect match without NHS number: do MCOB, BWψ and PCD agree?
Two matches on type 2: one *correct*	19	1) *Correct match* agreed on at least one available variable & *incorrect match* did not agree on any available variables (14 pairs) 2) *Correct match* disagreed on MCOB, agreed on 1 variable and 1 input variable was missing & *incorrect match* agreed on MCOB*, disagreed on 1 variable and 1 input variable was missing (2 pairs) 3) *Correct match* disagreed on 1 variable and 2 input variables were missing & *incorrect match* disagreed on 1 variable and 2 input variables were missing (1 pair) 4) Twin pairs: *correct match* agreed on MCOB, PCD, BW & *incorrect match* agreed on MCOB, PCD and disagreed on BW (2 pairs)
Two matches on type 2: both *incorrect*	1	Both possible matches disagreed on 3 variables
Three matches on type 2: one *correct*	1	*Correct match* agreed on at least one available variable & *incorrect matches* did not agree on any available variables
Two matches on type 4: both *incorrect#*	1	Both possible matches disagreed on 1 variable and 1 input variable was missing
Two matches on type 4: one *correct#*	6	1) *Correct match* agreed on at least one available variable & *incorrect match* did not agree on any available variables (5 pairs) 2) *Correct match* disagreed on MCOB and agreed on BW & *incorrect match* agreed on MCOB* and disagreed on BW (1 pair)
Three matches on type 4: one *correct#*	4	1) *Correct match* agreed on at least one available variable & *incorrect matches* did not agree on any available variables (3 pairs) 2) *Correct match* agreed on MCOB and BW & one *incorrect match* disagreed on MCOB and BW and the other *incorrect match* agreed on MCOB* and disagreed on BW (1 pair)

Notes: MDOB, mother's date of birth; PCD, mother's postcode district of residence at delivery; MCOB, mother's country of birth; BW, child's birth weight. Matches were identified as correct/incorrect if NHS number of the match found with the algorithm used without NHS number was the same/different as that found with the algorithm used with NHS number. *MCOB was UK. #Type 4 match includes PCD, therefore not included in the confirmation of correct/incorrect match. ψ within 10g.

4.3 Confirmation of matches made using the matching algorithm



Notes: PCD, mother's postcode district of residence at delivery; MCOB, mother's country of birth; BW, child's birth weight. *If agreed on MCOB and MCOB was UK then does not count as an agreement. #If twin or triplet, must agree on BW. BW considered to agree if within 10g.

Appendix 5 The main hospitals involved in the CHART study

Core hospitals (1st phase)

St Thomas' Hospital, London:

St Mary's Hospital, London:

Newham General Hospital, London:

St George's Hospital, London:

Royal Free Hospital, London:

Core hospitals (2nd phase)

Whipps Cross Hospital, London:

Sheffield Children's Hospital, Sheffield:

Leicester Royal Infirmary, Leicester:

Northwick Park Hospital, Harrow:

John Radcliffe Hospital, Oxford:

Birmingham Heartlands Hospital, Birmingham:

Other large hospitals

King's College Hospital, London:

Homerton University Hospital, London:

University Hospital Lewisham, London:

Chelsea and Westminster Hospital, London:

Appendix 6 The CHART study forms

6.1 Follow-up status form

6.2 Questionnaire

6.3 Parent's information sheet

6.4 Health professional's information sheet

Follow up of uninfected children born to HIV infected women (CHART)

For office use only
CSTU: MSTU: CONTACT: HOSP:

Please tick the appropriate statement(s) and sign this form.

1) ☐ The child's parent / carer has been contacted about this study.

Has the parent agreed to take part in the study?

☐ **Agreed**
How was consent given? Signed consent form ☐ Verbal consent ☐
Where is the consent form stored? ☐ Parent's notes in this clinic
☐ Child's notes in this clinic
☐ Elsewhere, specify.....

☐ **Not agreed** *If possible, please specify reason:* .....
.....

☐ **No reply** *Please explain:* .....
.....

2) The parent / carer has *not* been contacted about the study because:

☐ **The child has left the UK**

☐ **The child is lost to follow up** (because?.....)

☐ **The child / parent has been discharged from this clinic**
Please provide contact details for another health professional ***who is aware of the mother's HIV status:*** .....
.....

☐ **Other** *Please explain:*.....
.....

Signed ..... Date .....

Phone number.....

Email.....

Follow up of uninfected children born to HIV infected women (CHART) - Questionnaire for child's parent/carer

For office use only

CSTU	MSTU	CONTACT	HOSP

CONFIDENTIAL

1) **Child details.** Please supply any missing information, or make any corrections.

Date of birth ___/___/_____ ☐ Male ☐ Female Initials .....

Hospital no ..... **NHS no** .....

The last information we had on this child was dated ___/___/_____

This questionnaire should be completed by a health professional. Please tick boxes and complete as appropriate. The questions in bold print are to be addressed to the parent/carer. It may help to consult the child's Parent Held Record.

2) **Family. Who does the child currently live with?** (Tick all that apply)

☐ Mother ☐ Father ☐ Other relative, specify .....

If the child is not with his/her family, has s/he been:

☐ Fostered ☐ Adopted ☐ Other, specify .....

We would like to know how your child is doing in terms of general health, growth and development (since we last collected information on ___/___/_____), and we have some questions for you.

3) **Growth.** Please measure and/or weigh this child today.

Height (cm) ..... Weight (kg) ..... Date ___/___/_____

If this was not possible, please supply the child's most recent measured or estimated height and/or weight.

Height (cm) ..... Date ___/___/_____ ☐ Measured ☐ Estimated ☐ Not known

Weight (kg) ..... Date ___/___/_____ ☐ Measured ☐ Estimated ☐ Not known

4) **Developmental progress. Does your child attend:** (Tick all that apply)

☐ School ☐ Nursery ☐ Childminder ☐ Other, specify.....

Does your child receive any extra help at nursery or school? ☐ Not applicable ☐ No ☐ Yes, specify

.....

Does your child have any problems with, or do you have any concerns about their:

Walking/movement ☐ No ☐ Yes, specify .....

Speech ☐ No ☐ Yes, specify .....

Hearing/ears ☐ No ☐ Yes, specify .....

Sight/eyes ☐ No ☐ Yes, specify .....

Behaviour ☐ No ☐ Yes, specify .....

Other ☐ No ☐ Yes, specify .....

5) **General Health. Do you think your child is generally fit and healthy?** ☐ Yes ☐ No, specify

.....

.....

Since we last collected information, has your child been seen by your general practitioner, been referred to a specialist, been admitted to hospital or been taking on-going medication for: (Tick all that apply)

	General practitioner	Medical or other specialist	Hospital admission	On-going medication
Chest infections	☐	☐	☐	☐
Wheezing or asthma	☐	☐	☐	☐
Fits or convulsions	☐	☐	☐	☐
Other problems	☐	☐	☐	☐

Please give full details of all the conditions ticked. .....

.....

.....

.....

6) **Do you have any concerns about your child's growth, general health and progress that are not already mentioned above?**

☐ No ☐ Yes, specify .....

.....

7) Please thank the parent/carer for helping us with our study. The rest of the questions are for the health professional.

Form completed by _____ Date ___/___/_____ Occupation _____

Email _____ Telephone number _____

Where was the questionnaire completed? ☐ In clinic ☐ Over the phone ☐ Elsewhere, specify.....

Was the child present? ☐ No ☐ Yes

Was the child's Parent Held Record consulted while the questionnaire was completed? ☐ No ☐ Yes

Is there anything else about this child's health or development not mentioned above? ☐ No ☐ Yes, specify

.....

.....

Contact details of the health professional who should be sent child's next follow-up questionnaire.....

.....

CHART - Parent's information sheet

We would like to invite you to take part in a study (the CHART study) in which uninfected children born to mothers with HIV infection are being followed up.

Why do we need to follow up these children?
Most pregnant women with HIV take anti-HIV drugs during pregnancy and nearly all babies born to HIV infected women are given these drugs in the first few weeks of life. As a result most babies born to HIV infected women are not infected themselves. We do not think there are any serious side effects for children who are exposed to this treatment in the womb and in early life. However to make sure this is the case we would like to follow up all uninfected children born to mothers with HIV, whether or not their mothers had treatment in pregnancy.

How will this be done?
We would like to keep in touch with you and your child over the long term, and to collect information about your child's general health, growth and development once a year. One member of the clinic team currently responsible for your care or your child's care will complete a questionnaire with your help, at a convenient time. If your child has any serious health problem we may need to contact the specialists looking after him/her for further information. In this case we would ask your permission to do this.

Do I have to take part in the CHART study?
Taking part in this study is completely voluntary. You can decide, now or at a later stage, that you do not wish to take part. This will not affect any present or future treatment or care for you or your child.

What are the potential benefits?
This study will not bring any immediate benefits to your child. However it is important to find out whether using these anti-HIV drugs in pregnancy and infancy has any unexpected side effects, which could be avoided in the future. If any such problems are identified which require further treatment or tests, we would be able to contact you.

What are the risks and discomforts?
There are no physical risks or discomforts to you or your child from taking part in this study.

Who will have access to the questionnaire information?
The questionnaire will be forwarded to the researchers at the Institute of Child Health in London but it will not include your name. All information will be held in strict confidence.

Who do I speak to if any problems arise?
If you have any concerns about the study a member of the clinic team will be happy to discuss them with you.

For office use only

CSTU MSTU CONTACT HOSP

CHART - Consent form

For the parent/carer:

Please read and sign this form.

I have read the parent's information sheet on the CHART study.

I am willing to participate in the study and to answer some questions about my child's health.

Parent/carer: Signed.....Date.....

Health professional: Signed.....Date.....

Consent form to be
kept in the clinic

Follow up of uninfected children born to HIV infected women (CHART)
Health professional's information sheet

Background
The use of antiretroviral therapy (ART) during pregnancy for the prevention of vertical transmission of HIV has resulted in a substantial reduction in the number of HIV infected children. As pregnant women increasingly use this therapy and neonates are usually given ART in the first few weeks of life, a large number of uninfected children are being born that have been exposed to these drugs. However, there has been little research on any possible long-term adverse effects of *in utero* and neonatal exposure to antiretroviral drugs. It is important to monitor the effects of this exposure and to identify and investigate any possible side effects.

Follow up of children exposed to antiretroviral therapy in pregnancy
In the UK and Ireland, pregnant women known to be HIV infected are reported through the Royal College of Obstetricians and Gynaecologists (RCOG) to the National Study of HIV in Pregnancy and Childhood (NSHPC), based at the Institute of Child Health in London. In a parallel scheme, paediatric cases of HIV infection and children born to HIV infected women are notified through the British Paediatric Surveillance Unit (BPSU) of the Royal College of Paediatrics and Child Health, and are followed up to ascertain infection status and progression to AIDS. The reports are linked and contribute the paediatric data to the overall surveillance of HIV and AIDS.

Originally, once children born to HIV infected women were confirmed to be uninfected, no further follow up information was sought. For infected children (and those of indeterminate status) annual follow up information was requested from notifying paediatricians.

We are now extending annual follow up in the UK by collecting information on children who are confirmed uninfected (the CHART study). This will be done by a health professional completing a questionnaire on the child's general health, growth and development in consultation with the child's parent/carer. In the unlikely event of a major health problem being identified, we may need further medical information on the child from their records within the unit. If specialists outside this team need to be contacted for information, we will ask for parental permission to do so.

In most cases the information on the antiretroviral therapy exposure will already have been prospectively obtained through the obstetric and paediatric surveillance.

Parental consent
The health professional (obstetrician or genitourinary physician) looking after the woman during pregnancy should have already discussed the risks and benefits of therapy with her and indicated that she will be asked for permission for her uninfected child to be followed up.

On the questionnaire, there is space for further details about the child's general health, growth and development. The health professional should use this where applicable.

Each follow up questionnaire relates to the period since the last one was completed, or since confirmation of uninfected status if it is the first. The health professional may want to refer to the previous questionnaire to avoid duplicating information.

Notes on completing the questionnaire

Box 1- We will fill in information that we have to identify the child. The health professional should supply any missing information, or make any corrections to this. Information is being sought relating to the period since the date specified. Please supply the child's NHS number if available.

Box 2- The relatives that the child lives with should be specified. If the child does not live with their own family, please give details of their current carer.

Box 3- The health professional should weigh and measure the child (without shoes and outdoor clothing) when the questionnaire is filled in. If this is not possible, they should supply the most recent measured or estimated height and weight. This may be taken from the Parent Held Record or the child's clinic records.

Box 4- We would like to know about any extra help that the child receives relating to their learning and development. If the child has problems with walking, speech, hearing, sight or behaviour for which a specialist opinion has been sought or the parent/carer has concerns, please give details.

Box 5- We are interested in any problems that have required medical attention, a stay in hospital or on-going medication. We would like to know the frequency with which these serious illnesses have occurred or whether they are a chronic condition. Please supply the names and addresses of the relevant hospitals or specialists.

Box 6- This allows the parent/carer to mention any concerns they have that have not been included in the rest of the questionnaire.

Box 7- This is for the health professional to complete. If they have any information on the child's health, growth and development that has not been given in the rest of the questionnaire, they should include it here. It is important to date and sign the form and let us know to whom we should send the next follow up questionnaire.

The top copy of the questionnaire should be returned in the freepost envelope to: Claire Hankin, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health . The bottom copy should be kept in the parent or child's notes.

The parent/carer should be encouraged to bring in their Parent Held Record, which may assist in the completion of the questionnaire. Ideally this questionnaire will be

Appendix 7 The health professional survey questionnaire

Antiretroviral therapy-exposed uninfected children born to HIV-infected women

A questionnaire for health professionals

Name..... Position.....

Hospital..... Date completed.....

When the CHART study was established in 2002, part of the remit was to assess the feasibility of following up uninfected children. We would like to know what your clinic practice is regarding uninfected children. We would also like to hear about your experience with the CHART study, particularly how you approached the families and issues that you feel may have affected enrolment.

A) CLINIC INFORMATION

1) Approximately how many uninfected children born to HIV-infected women are seen in your clinics?

..... per month/year *(delete as appropriate)*

2) What best describes the clinic where uninfected children are generally seen?

- General paediatric clinic ☐
- Paediatric infectious diseases clinic ☐
- Paediatric HIV clinic ☐
- Family HIV clinic (for children and adults) ☐
- Other, *specify*..... ☐

3) Do you regularly discuss issues relating to uninfected children with colleagues in the following departments in your hospital?

	Yes	No
Genitourinary/Sexual Health department	☐	☐
Antenatal/Obstetric department	☐	☐
Other, *specify*.....	☐	☐

.....

4) What is your routine clinic follow up protocol for a child born to a woman diagnosed with HIV before or during delivery? *(e.g. 6 weeks, 3 months etc.)*

.....

.....

9a) How have you usually approached parents/carers about the CHART study?
9b) How often have you used other ways to approach parents/carers about the CHART study?

	9a) *(tick one)*	9b) *(tick all that apply)*		
	Usually	**Sometimes**	**Hardly ever**	**Never**
At child's confirmatory test	☐	☐	☐	☐
Opportunistically in paediatric clinic	☐	☐	☐	☐
Opportunistically in adult clinic	☐	☐	☐	☐
Over the phone	☐	☐	☐	☐
In the parent/carer's home	☐	☐	☐	☐
Other, *specify*.....	☐	☐	☐	☐

10) How often have the following situations made contacting parents/carers about the CHART study difficult?

	Frequently	Sometimes	Hardly ever	Never
Regularly DNA scheduled appointments	☐	☐	☐	☐
Lost contact with family	☐	☐	☐	☐
Family known to have left the UK	☐	☐	☐	☐
Difficult family circumstances	☐	☐	☐	☐
Child discharged from clinic	☐	☐	☐	☐
Lack of clinic staff time	☐	☐	☐	☐
Other, *specify*.....	☐	☐	☐	☐

.....

11) How often have the following issues played a part in parents/carers agreeing to take part in the CHART study?

	Frequently	Sometimes	Hardly ever	Never
Concern over the safety of the antiretroviral therapy	☐	☐	☐	☐
Wanting to keep in contact with health services	☐	☐	☐	☐
Feeling uncomfortable about refusing	☐	☐	☐	☐
Other, *specify*.....	☐	☐	☐	☐

.....

.....

15) When do you think parents/carers should be asked for permission for the child to be included in follow-up?

During pregnancy ☐

At birth ☐

When child is known to be uninfected ☐

Other, *specify*..... ☐

.....

.....

In the parent/carer questionnaire we describe several different ways of following up uninfected children, including the CHART protocol. Please read the four options and answer the questions on the following page. Any new system would have to be approved through the appropriate channels.

OPTION A (CLINIC CONTACT)

- You would ask the parent/carer and/or the child to come to the family or paediatric clinic once a year.
- You would ask them general questions about the child's health.
- The answers would be put on a form and sent to us. Neither the parent/carer's name nor the child's name would be on the form.
- The parent/carer would need to inform you of any change in their contact details.

OPTION B (TELEPHONE CONTACT)

- You would telephone the parent/carer once a year and would ask them general questions about the child's health.
- The answers would be put on a form and sent to us. Neither the parent/carer's name nor the child's name would be on the form.
- The parent/carer would not need to attend the clinic to take part, but they would need to inform you of any change in their telephone number.

OPTION C (POSTAL CONTACT)

- You would give us the parent/carer's contact details when the child was discharged. We would keep these in strict confidence.
- We would send the parent/carer a short form about the child's health once a year, for them to complete and send back to us.
- There would be no reference to HIV on anything they were sent.
- They would need to inform us of any change in their address.

OPTION D (NO DIRECT CONTACT)

- We would not need to have any regular direct contact with the parent/carer or the child and we would not know the parent/carer's or the child's name or address.
- Every child in the UK is given an NHS number at birth. You would give us the child's NHS number which we could relate to routinely available health information.
- The parent/carer would not have to keep in contact with the clinic after the child was discharged.

Appendix 8 Comments from the health professional survey questionnaires

Comments on the CHART study

"Difficulties with keeping in touch with families, often move frequently. Also, most families feel happy at 18/12 when discharged, feel bad asking them to keep in touch for longer." [Respondent 12]

"Families are often busy may need to phone several times after a while you feel bad hounding them" [Respondent 14]

"When parents are discharged they want to get away from us as fast as possible and start to live a 'normal' life. As for us contacting them, they stress out at us if a new partner is on the scene and knows nothing about the mother's status. These are things I have had to worry about and some mothers have put the phone down on me saying 'never contact me again'." [Respondent 15]

"People do not think through what it means- i.e. they do want to help/be followed up but change address, phones etc and CHART is not on their minds once they move on with children growing up. I have never spoken to anyone who didn't think it important in principle; it's the intrusion in their lives which puts them off." [Respondent 14]

"Two distinct groups of patients exist: 1- who would like engaging medical contact with non specific concerns. 2- who would want to cut off with us as soon as possible." [Respondent 16]

"This was a very important study, the difficulty for us health professionals was trying to contact some of the carers/parents, due to high mobility of our clients. With older children, parents/carers were very suspicious when we contacted them, and will often DNA appointments." [Respondent 17]

"In retrospect I should have discussed it more regularly at clinic visits but many had only had 1 or 2 negative tests and were indeterminate status. By the time they are known to be negative they are then not in regular contact until 18/12 and many of these are lost to follow up/move." [Respondent 04]

"To enrol before 3/12 old so have opportunity to discuss while still in close contact." [Respondent 05]

"Problem for paeds is we discharge them after the 12-15/12 bloods, completing a form for you then. Our HIV clinic have agreed to continue handing out Qs." [Respondent 29]

"I apologise for not recruiting my children. This was due to fact I don't routinely see after 18/12. Did explore getting GU team to do it- interested but I failed to take it forward fast enough. [Respondent 30]

"Two major barriers to enrolling into the study: 1. family discharged from clinic and do not want on-going involvement or move/are moved away. 2. lack of time and resources to undertake extra work commitment to this." [Respondent 06]

"Despite relatively simple study, this has proved difficult to carry out here with poor secretarial resources and DNA appointments. Clinics already very busy." [Respondent 37]

"Although it is difficult for us to have time to follow up these children and to keep track of the families- I think it would be virtually impossible for centres e.g. out of London- who do not have dedicated paed HIV staff." [Respondent 27]

"We didn't encounter many problems because of our small cohort of families- they were all more than willing to help." [Respondent 40]

"The entire workload has rested with a single paediatric consultant (myself) and the paperwork and parent liaison has been a nightmare. We are a particularly busy unit and a smaller unit with fewer children would find this a lot easier." [Respondent 09]

"I think it is important to carry on even though I am bad at filling out the forms." [Respondent 13]

"All but one agreed. Reasons for agreeing not discussed but seemed to understand need for checking no unexpected side effects." [Respondent 29]

"Forms have been relatively easy to complete and generally can be done so during regular consultation time." [Respondent 08]

"If there are going to be long term and subtle side effects, CHART questionnaire is too simple to unearth these. Overall I feel slightly uneasy bringing children all the way to the clinic and send back after a few simple questions. So I also examine them thoroughly." [Respondent 16]

"I would be happy to continue recruiting into the study as I feel the data that is generated will guide service development." [Respondent 22]

Comments on the follow-up options presented in the questionnaire

"I think the concept of long term follow-up needs to be raised when women are being either started on treatment or when/during pregnancy and then reiterated at all other visits for baby follow up i.e. birth, 6 weeks, 3 months and 18 months." [Respondent 14]

"Parents could be informed about study during clinic visits so that when child is uninfected they will be expecting follow up studies." [Respondent 18]

"Options A-C all unfunded at present. I have warned parents that long term contact may occur." [Respondent 11]

"I would prefer that follow-up did not take place from clinic. Difficulties in dedicating time etc." [Respondent 12]

"All OK- but option A is not achievable for 100% of the families therefore is it useful as so many are lost to follow up." [Respondent 27]

"There is a significant issue with respect to clinician and clinic time. As length of follow up proposed increases number of contacts will grow. I deal with relatively low numbers but for a large patient load this is likely to become unmanageable. Personally I find it difficult to allocate outpatient slots as I am seeing these patients in the context of a busy neonatal follow up programme and as patient numbers increase this problem will escalate. A non clinic contact is therefore attractive. I think phone and post contacts may well be difficult to achieve given the mobility of many of these patients." [Respondent 28]

"Problem with postal contact is that may be opened by another family member- many asylum seekers in multioccupation. Even if no mention of HIV it may trigger awkward questions. My own experience of postal follow up would suggest you'll get very few answers not because of genuine refusal but just never received it. D is probably best option if there is enough useful info held centrally but no good if only tracks mortality." [Respondent 29]

"Would be delighted to give you details to follow families directly- appreciate this needs different ethics agreement." [Respondent 37]

"Seeing in clinic is ideal but at present to do this would involve me using 2 whole clinics for this and I do not think our Trust would agree to this." [Respondent 30]

"Re option C- I would be happy to ask families at last visit when uninfected but I do not think you will get good response as it is not something they can continue to feel 100% commitment to and that's what you need- other things become more important naturally over time" [Respondent 14]

Appendix 9 The hospitals involved in the parent and carer survey

Chelsea and Westminster Hospital, London:

Homerton University Hospital, London:

King's College Hospital, London:

Newham General Hospital, London:

Northampton General Hospital, Northampton:

Princess Anne Hospital, Southampton:

Princess Royal Maternity Hospital, Glasgow:

St George's Hospital, London:

St James' University Hospital, Leeds:

St Thomas' Hospital, London:

University Hospital of Wales, Cardiff:

Wexham Park Hospital, Slough:

Appendix 10 The parent and carer survey information sheet

Parents and carers' views on long-term follow-up
INFORMATION SHEET

We are researchers at the Institute of Child Health in London and we would like to ask you to complete a short questionnaire about you and your child. We would like to know your views on the long-term follow-up of uninfected children born to women with HIV.

What do we mean by "long-term follow-up"?
We are trying to find the best way to keep in contact with uninfected children and their families throughout childhood.

Why should we follow up uninfected children?
Most children born to HIV infected women in the UK are themselves uninfected. For example, in 2001 there were about 500 children born in the UK to HIV infected women. Of these about 475 were uninfected.

Most uninfected children have been exposed to anti-HIV drugs because their mother took them when she was pregnant. It is unlikely that these drugs have serious side effects. However, we want to ask your views on ways to keep in contact with these children in case any side effects are found in the future.

Who should complete the questionnaire?
A parent or a carer (such as a grandparent) of an uninfected child born in the UK to an HIV infected woman who took anti-HIV drugs when she was pregnant.

Who would see the completed questionnaire?
Only the researchers at the Institute of Child Health would see the completed questionnaire. You will NOT be asked for your name. No information about you or your child collected by the clinic would be linked to anything you write on the questionnaire.

Do I have to take part?
No. Taking part is completely voluntary. If you do not want to take part, your own care and the care of your child will not be affected in any way. However completing this questionnaire means that you can tell us what you think about how we should keep in contact with these children.

How to contact one of the researchers:
The contact person is: Claire Hankin, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health,

If you have decided to complete the questionnaire, please then put it in the envelope provided, seal it and return it to the researcher in the clinic.

We do NOT need to know your name. Please do NOT write your name on the questionnaire.

Appendix 11 The parent and carer survey questionnaire

Parents and carers' views on long-term follow-up
ANONYMOUS QUESTIONNAIRE

Date: ____/____/____ Clinic:

SECTION 1: YOU AND YOUR CHILD

1) How many children who were born to an HIV infected woman are in your care?

.....

2) For the child/children, please tell us their age, their HIV infection status and whether they were born in the UK. *Continue on last page if necessary*

Age	**Infection status**			**Born in the UK?**	
	Infected	*Uninfected*	*Not known*	*Yes*	*No*
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐
.....	☐	☐	☐	☐	☐

3) What is your relationship to the child/children? *Tick all that apply*

- Mother ☐
- Father ☐
- Aunt/Uncle ☐
- Grandparent ☐
- Adoptive/Foster parent ☐
- Other (please specify) ☐ .....

4) Which country were <u>you</u> born in? .....

5) Looking to the future, do you expect the child/children to continue living in the UK?

- Yes ☐
- No ☐ **If NO**, when might they leave the UK? .....

6) How often do you visit the <u>family or paediatric clinic</u> for the child/children's care?

- No longer visit clinic ☐
- Less than once a year ☐
- 1-4 times a year ☐
- More than 4 times a year ☐

7) Have you always visited the same <u>family or paediatric clinic</u> with the child/children?

- Yes ☐
- No ☐ **If NO**, how many have you been to?.....

8) Do you ever take the child/children to a GP?

- Yes ☐
- No ☐ ***If NO**, go to question 10*

11) Parental permission would be needed before a child was included in options A, B or C (direct contact).

If we used option D (no direct contact), do you think parental permission would also be needed?

Yes ☐
No ☐

12) When do you think parents/carers should be asked for permission for the child to be included in follow-up?

During pregnancy ☐
At birth ☐
When child is known to be uninfected ☐
Other *(give details below)* ☐

.....
.....

13) How much do you agree with the following statement:

It is important to follow up uninfected children to see if there are any side effects from anti-HIV drugs

Strongly agree ☐
Agree ☐
Disagree ☐
Strongly disagree ☐

14) Which option(s) would be acceptable to you?

Tick one box for each option

	Yes	No
Option A (Clinic contact)	☐	☐
Option B (Telephone contact)	☐	☐
Option C (Postal contact)	☐	☐
Option D (No direct contact)	☐	☐

15) Do you strongly object to any of the options?

Yes ☐
No ☐ ***If NO**, go to question 17*

16) Which option(s) do you object to, and why? *Continue overleaf if necessary*

.....
.....
.....
.....

Appendix 12 Comments from the parent and carer survey questionnaires

Importance of follow-up

"I think it is a good idea following up these children because it shows you have their interest at heart and would like to know and help them if they do get any side effects from the drugs." [Mother of two children (aged 1 and 7 years)]

"We don't know the outcome of these drugs so we shouldn't hesitate with investigations." [Father of four children (aged 1, 4, 14 and 15 years)]

"I strongly feel that it's very important to follow up on our children since nobody knows what the long term effects of these drugs can be." [Mother of two children (aged 3 and 7 years)]

"I think it's a good idea because they are strong drugs and it's known that pregnant women shouldn't take drugs. Nobody knows what kind of effects the drugs have in the future or not. This would enable them to help other children." [Mother of two children (aged 3 months and 2 years)]

"I think it's important because you don't know the side effects. I think about it sometimes but not very often." [Mother of three children (aged 1, 3 and 6 years)]

"Sometimes when my son is ill I think all the negative things but if he's followed up my mind can be clear. I think following them up is a good idea." [Mother of one child (aged 1 year)]

Need for follow-up?

"If they think there are problems then it [follow-up] *is important. If there aren't side effects then it is wasting time."* [Mother of four children (aged 2, 3, 11 and 14 years)]

"When the baby is healthy and doesn't have any problems she doesn't need to be coming to the hospital. She's doing well but you never know if she will get a problem." [Mother of one child (aged 3 months)]

"When you are pregnant you are worried about the virus passing to baby and not strongly about the effects of the drugs." [Mother of one child (aged 3 months)]

"If child is uninfected I'd like to leave it at that, rather than being reminded of the illness." [Mother of one child (aged 6 months)]

Specific child health concerns

"I sometimes think she's too skinny and wonder if it's the drugs. My other babies are chubby." [Mother of three children (aged 1, 3 and 12 years)]

"I think once the drugs have come out of the child's system I would have thought there would be no such risk again, but for children could it make them as teenagers not being able to have children later on in life?" [Mother of two children (aged 2 and 4 years)]

Disclosure and confidentiality

"Although I strongly support research into the follow-up of children exposed to anti HIV drugs I am currently unwilling to give my permission for this to happen as I feel that my decision of when or whether to tell my child about my HIV status could be taken out of my hands. If you can assure me this won't happen I will happily comply." [Mother of one child (aged 1 year)]

"I think that is important to do a follow up, but at the same time if the child is uninfected it is difficult for them to maybe accept or understand about all this, so would be better to leave this subject (or burden as it is at the moment) out of their life." [Mother of one child (aged 2 years)]

"I'm happy about the system they have now, the advice and the care that you get when you are pregnant. But I'm not happy about coming back to the clinic because they [children] *will start asking questions and I'm not ready to tell them about my situation until they are 16."* [Mother of four children (aged 2, 3, 11 and 14 years)]

"If baby is negative until 3rd test, I as a mother won't be able to explain what happen (prefer kept a secret) but if risks happens on his health then I decide then how to explain to him and what to do." [Mother of one child (aged 1 year)]

"I think once a teenager reaches a certain age I not sure I would tell my children I have HIV if I'm still alive so I would not want to harm or scare them in any way but that's a long way ahead of me, things change." [Mother of two children (aged 2 and 4 years)]

"I feel that keep the child under checks would bring some conflict. In my opinion I have chosen not to disclose my HIV status to my family. Therefore I do not feel comfortable if my children were to know my status from continuous check-up. [Mother of one child (aged 3 years)]

"I wouldn't want this to be hanging over his head because I am HIV. I want him to be normal." [Mother of three children (aged 6, 14 and 17 years)]

"Am happy to help with research if totally anonymous." [Mother of one child (aged 1 year)]

"I think that GPs must be aware of any follow-up programme. I know some families with HIV are not always comfortable with this- but personally I find it crucial to keep our family health care as 'normal' as possible- less explaining, and I think less stigmatised." [Mother of one child (aged 6 years)]

Timing of follow-up

"I want to know in pregnancy what kind of follow up is coming up." [Mother of one child (aged 1 year)]

"When you ask parents depends on how it's done. It depends on how you supply the information. If someone is struggling with their pregnancy you're not going to get the best feedback. It might not be appropriate to ask them when they are pregnant." [Father of one child (aged 1 year)]

"I wouldn't have time to bring him to clinic because most times I come on Tuesdays and he's at school." [Mother of three children (aged 6, 14, and 17 years)]

Contact via parent/carer or direct with child/young person?

Age of child/young person

"Ask the person themselves once they are 18. They will know about their parents' illness when they are grown up." [Mother of one child (aged 3 months)]

"Depends on the age of the child. The parents should be responsible enough to explain to the child at a reasonable age. By the time they are 16 they should know about the parent's diagnosis. I would then be happy for them to be contacted directly." [Mother of two children (aged 6 weeks and 5 years)]

"I think that when they are still young it would be important to contact the carer. But once they're more mature then it's fine to contact them without the carer there." [Mother of two children (aged 1 and 7 years)]

"Once they are an adult you can contact them directly." [Father of one child (aged 3 months)]

"Depending on age. Some teenage children prefer their independence- yes- direct contact can be better." [Mother of four children (aged 3, 10, 14 and 16 years)]

"Contact still through the parents even when they are adults." [Mother of three children (aged 3, 8 and 9 years)]

"Should still contact the parent even when the child is older." [Mother of one child (aged 5 months)]

Permission

"Go direct to child. No need to ask for permission from mum." [Mother of one child (aged 2 years)]

"Researcher or clinic should only contact young person directly once permission has been sought from parent. It should be done in consultation with family doctor." [Mother of one child (aged 6 years)]

Contacting child/young person

"The mother should be contacted rather than him directly. She's known him from birth." [Mother of three children (aged 1, 3 and 6 years)]

"I wouldn't want someone contacting my child. I'd rather it be left for me to be in control of it." [Mother of one child (aged 1 year)]

"I would like to know first. You might go to him first and he might not like it. I don't want to do anything to upset my child." [Mother of one child (aged 1 year)]

"The parent should be contacted first, no matter what the situation is, then the parent can speak to him/her about it in private. I think it better, if it comes from the parent." [Mother of two children (aged 2 and 6 years)]

Child/young person's choice

"That's for him to decide. I will tell him what happened- that I took the drugs- and he can decide what to do for his future." [Mother of two children (aged 2 and 16 years)]

"I don't know. If they are grown up then it's up to them." [Mother of four children (aged 2, 3, 11 and 14 years)]

Vital status of parent

"If I'm still alive I want it through me but if she knows then it can be through her." [Mother of three children (aged 1, 3 and 12 years)]

"It should be up to the parent/carer to tell the clinic or researchers when they can contact the young person. A young person should only be contacted if the parents are no longer around (dead)." [Mother of three children (aged 1, 3 and 8 years)]

"If the monitoring can continue I don't have a problem, but I wouldn't want him to be contacted directly. If we are alive let it pass through us." [Father of four children (aged 1, 4, 14, and 15 years)]

Disclosure to child/young person

"It depends on whether the carer or parent have been open about it the child can be contacted directly but if not the parent has to discuss it first with the child before he is called in to be seen or talk by the doctor." [Mother of two children (aged 1 and 8 years)]

"I think it should be up to the parent to tell the clinic if they can contact the young person as it would necessitate the mother's disclosure of her own HIV status and this is a very personal, individual matter." [Mother of one child (aged 1 year)]

"This entirely depends on how much is known by the children about parent's condition. Each case is individual but no contact without prior permission should ever occur." [Father of three children (aged 1, 2 and 12 years)]

"The clinic or researchers must not under any circumstances break the news of a parents infection to a young person. I think it is the parents/carer responsibility to do so when they feel the time is right." [Mother of two children (aged 1 and 3 years)]

"Contacting the parents is better because he doesn't know about the Mum's illness." [Father of two children (aged 2 and 6 years)]

"It should be up to the parent to tell the clinic when appropriate, as many people may not want to let their children know if they remain uninfected." [Mother of one child (aged 4 months)]